Dementia risk in the population over time: potential for primary prevention and intervention

This dissertation is submitted for the degree of Doctor of Philosophy by

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Date of submission: November 2018

Declaration

This dissertation is the result of my own work and includes nothing which is the outcome of work done in collaboration except as declared in the Preface and specified in the text. Material from chapters 4, 5 and 6 are currently being prepared for publication but have not yet been submitted. I conducted the statistical analyses for the individual chapters.

It is not substantially the same as any that I have submitted, or, is being concurrently submitted for a degree or diploma or other qualification at the University of Cambridge or any other University or similar institution except as declared in the Preface and specified in the text. I further state that no substantial part of my dissertation has already been submitted, or, is being concurrently submitted for any such degree, diploma or other qualification at the University of Cambridge or any other University or similar institution except as declared in the Preface and specified in the text.

It does not exceed the prescribed 60,000 word limit (excluding tables, figures, references and appendices) set by the School of Clinical Medicine Degree Committee.

Holly Bennett

16th November 2018

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Thesis Summary

Dementia prevalence and incidence has decreased over time in the UK. This will in part be due to changes in dementia risk. Although dementia risk has been studied extensively, there is relatively little literature on change in dementia risk over time and current evidence is conflicting. If the risk factor profile of dementia changed this would impact prevention and intervention strategies as well as future health service and care needs. This thesis explores the change in dementia risk factor profiles in the UK population, changes across time and implications.

Risk factor prevalence and their association with dementia were examined using the two Cognitive Function and Ageing Studies (CFAS I and II), both large UK population based studies. Baseline interviews for CFAS I began in 1991 and for CFAS II in 2008 with identical study dementia diagnosis to provide reliable estimates of dementia risk. Inverse probability weights were used to adjust for initial non-response and multiple imputation was used to account for item non-response. Relative risk of incident dementia was measured by Poisson regression accounting for person-years. Changes in prevalence and relative risk would result in changes to Population Attributable Fractions (PAFs) of dementia that measure the proportion of incident dementia cases associated with risk factors. Three combined PAF models were considered. An early/midlife model, a health condition model and a proximal model. The full model included the risk factors from all three models. To explore whether dementia prevalence will continue to decline in the future taking into account current risk factor trends, number of people with dementia and dementia prevalence in the UK were forecasted until 2040. Considering the possibility of population interventions, higher education was used as a case example. A systematic review was first conducted, followed by analysis on lifelong education and cognition using Structural Equation Modelling in a further population based study that focused on healthy ageing (the Cambridge Centre for Ageing and Neuroscience (CamCAN) study, initiated 2010).

The risk results suggested that having an unskilled occupation compared to a semi-skilled occupation and currently smoking compared to never smoking were associated with increased risk of dementia in CFAS II but not CFAS I. Other associations remained stable with stroke,

loneliness and functional impairment associated with increased dementia risk and higher education with decreased dementia risk in both studies. There were more changes in prevalence of risk factors over time, the largest changes being in prevalence of education, smoking, hypertension and diabetes. The fully combined PAF model was associated with a greater proportion of incident dementia cases in CFAS II than in CFAS I. This was mainly due to an increase in the proportion of incident dementia cases associated with proximal risk factors. Early/midlife risk factors and health condition risk factors were associated with similar proportions of incident dementia cases in both studies. In the future, number of people with dementia and dementia prevalence are expected to increase. However, increases in education and prevention of midlife obesity and stroke could greatly attenuate expected future dementia cases. Finally, current literature on lifelong education and cognition provide support for a role of higher education as an intervention. The CamCAN analysis addressed some of the gaps in the literature and suggested that education in later life in addition to higher education in young adulthood was associated with better cognition.

These findings add to the growing literature on dementia risk. The dementia risk profile has changed over time indicating a shift towards proximal risk factors for prevention. Throughout, higher education has been highlighted as an important protective factor and increasing higher education could potentially attenuate future expected dementia cases. To more accurately estimate the impact of increasing higher education on future dementia, longitudinal models accounting for mortality based on data from the UK are essential.

Papers and Presentations

- Papers in preparation

Holly Q Bennett, Carol Brayne, Fiona E Matthews. *Does profile of dementia risk change across generations? Findings from two cohorts*

Holly Q Bennett, Carol Brayne, Fiona E Matthews. *Determining areas for dementia prevention at a population level from a large prospective cohort study using population attributable fractions*

Holly Q Bennett, Andrew Kingston, Carol Jagger, Carol Brayne, Fiona E Matthews. *Forecasting dementia cases and prevalence in the UK to 2040 taking into account risk factor trends and population ageing*

- Oral and poster presentations

31/10/17 CFAS Doctoral Training Centre Scientific day, Newcastle, UK

ORAL "Education and occupation differences and their impact on dementia in CFAS I and II"

17/7/17 Alzheimer's Association International Conference, London, UK

ORAL "Forecasting dementia in the UK to 2030"

5/5/17 TRENDS conference, Washington, USA

ORAL "Forecasting dementia in the UK to 2030"

21/6/16 CLAHRC EoE Summer Event, Hertford, UK

POSTER 'Dementia risk in the population over time'

Abbreviations

ACE-R – Addenbrooke's Cognitive Examination Revised

ADL – Activities of Daily Living

AGECAT – Automated Geriatric Examination for Computer Assisted Taxonomy

ALPHA – Ageing in Liverpool Project – Health Aspects study

BMI – Body Mass Index

CamCAN – the Cambridge Centre for Ageing and Neuroscience study

CAM-COG – Cambridge Cognitive Examination

CFAS I – Medical Research Council Cognitive Function and Ageing Study restricted to thee centres to allow comparison with CFAS II

CFAS II – Second Cognitive Function and Ageing Study

CI – Confidence Interval

DALY – Disability Adjusted Life Year

EAF – Exposed Attributable Fraction

EAR – Exposed Attributable Risk

ELSA – English Longitudinal Study of Ageing

EPIC-EPAQ2 – European Prospective into Cancer Study-Norfolk Physical Activity Questionnaire

FIML – Full Information Maximum Likelihood

FINGER – Finnish Geriatric Intervention Study to Prevent Cognitive Impairment

GHS – General Household Survey

GMM – Growth Mixture Modelling

GMS – Geriatric Mental State

GP – General Practice

HAS – History and Aetiology schedule

HATICE – Healthy Ageing Through Internet Counselling in the Elderly

HSE – Health Survey for England

IADL – Instrumental Activities of Daily Living

In-MINDD – Innovative Midlife Intervention for Dementia Deterrence

IRR – Incidence Rate Ratio

LEQ – Lifetime of Experiences Questionaire

MAPT – Multidomain Approach for Preventing Alzheimer's Disease

MEG – Magnetoencephalography

MMSE – Mini Mental State Examination

MRC CFAS – Medical Research Council Cognitive Function and Ageing Study

MRI – Magnetic Resonance Imaging

NHS – National Health Service

ONS – Office for National Statistics

PAF – Population Attributable Fraction

PAR – Population Attributable Risk

PreDIVA – Prevention of Dementia by Intensive Vascular Care

PSU – Primary Sampling Units

NART – National Adult Reading Test

RR – Relative Risk

SEM – Structural Equation Model

THBP – Tasmanian Healthy Brain Project

WAIS – Wechsler Adult Intelligence Score

WHO – World Health Organisation

WMS-III UK – Wechsler Memory Scale Third UK edition

WRAT – Wide Range Achievement Test

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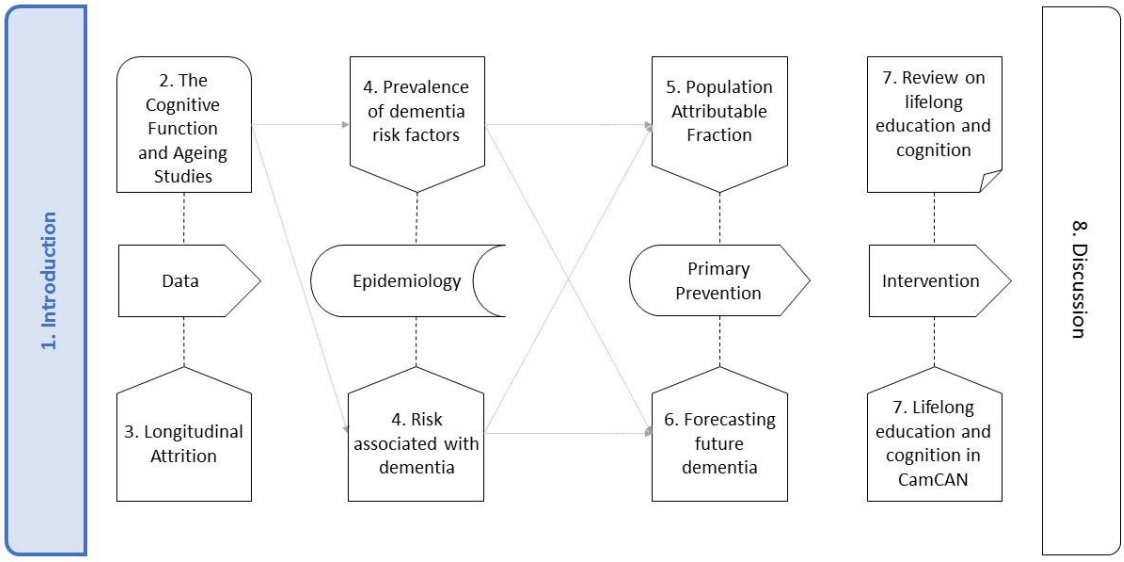
Chapter 1: Introduction

1.1 Chapter overview

The aim of this chapter is to introduce the dissertation and provide a background on dementia research and risk. To do this the introduction provides:

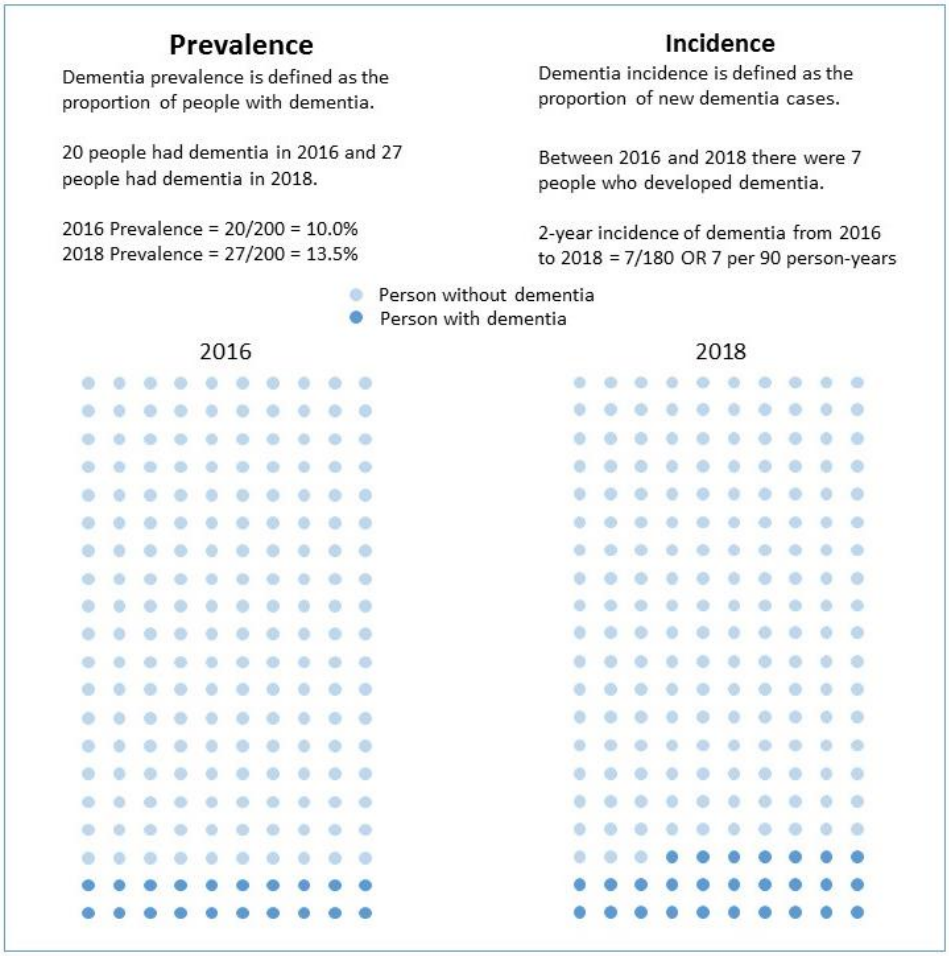
i. A rationale for the thesis structure
ii. A background on dementia research
iii. A background on risk associated with dementia
iv. An outline of the aims and objectives of this thesis



1.2 Introduction to dementia research

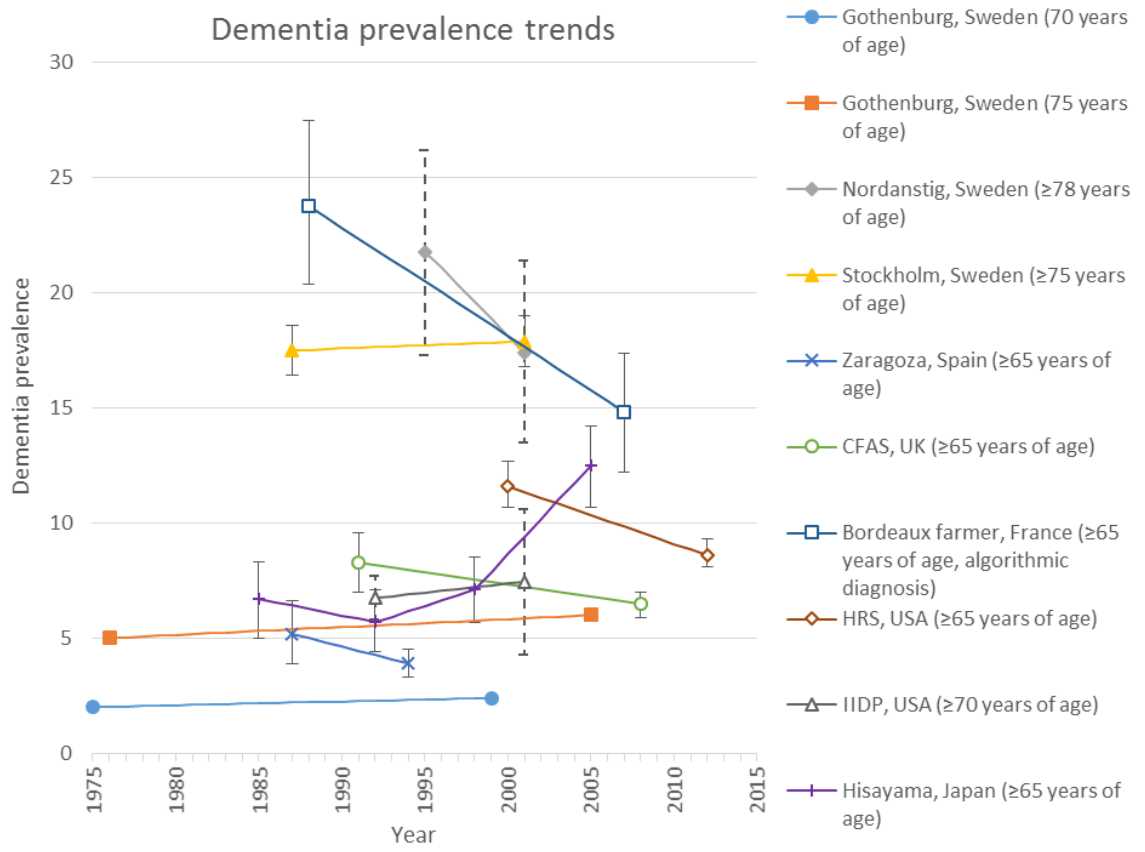
Dementia presents as cognitive and functional impairment and in its later stages prevents people from carrying out basic activities of daily living without assistance (toileting, eating). Although some cases present earlier in life, dementia mainly affects older people and is one of the leading causes of moving into care and nursing homes, where dementia prevalence is higher than in the community [1]. Alzheimer's Research UK currently estimates there to be 955,000 people living with dementia in the UK [2, 3] whilst others suggest this is probably lower at closer to 800,000 [4]. Alzheimer's research UK estimates there are 209,600 incident cases of dementia each year in the UK [5, 6]. Evidence shows that dementia prevalence increases with age [7] and that in the UK the population aged 65 years and older is growing [8]. Despite this, studies have shown that in the UK age specific dementia prevalence [7] and incidence [6] are declining over time. For a fictional example of prevalence and incidence see Figure 1.1.

Figure 1.1: Description of dementia prevalence and dementia incidence



Studies with similar methodology and dementia diagnosis show that dementia prevalence trends are mainly stable or declining over time [9-11]. Figure 1.2 gives total dementia prevalence at different time points for Sweden, Spain, the UK, France, the USA and Japan with 95% confidence intervals if provided. Confidence intervals for some estimates are wide but still give a sense of the general direction. In Sweden results from Gothenburg [12] and Stockholm [13] suggest a stable or gently increasing prevalence, however, estimates from Nordanstig suggest otherwise [14]. Dementia prevalence in Spain [15] and France [16] is declining over time. Results differ in the USA with opposite trends from two separate studies [17, 18]. A study from Japan estimated dementia prevalence at more than two time points. After a brief decline, dementia prevalence started increasing over time [19].

Figure 1.2: Dementia prevalence trends over time in different countries, 95% confidence intervals given if provided. As confidence intervals for the Nordanstig, Sweden and IIDP, USA overlap with others, their confidence intervals are dotted. Data from [9] and individually from Sweden [12-14], Spain [15], the UK [7], France [16], the USA [17, 18] and Japan [19].

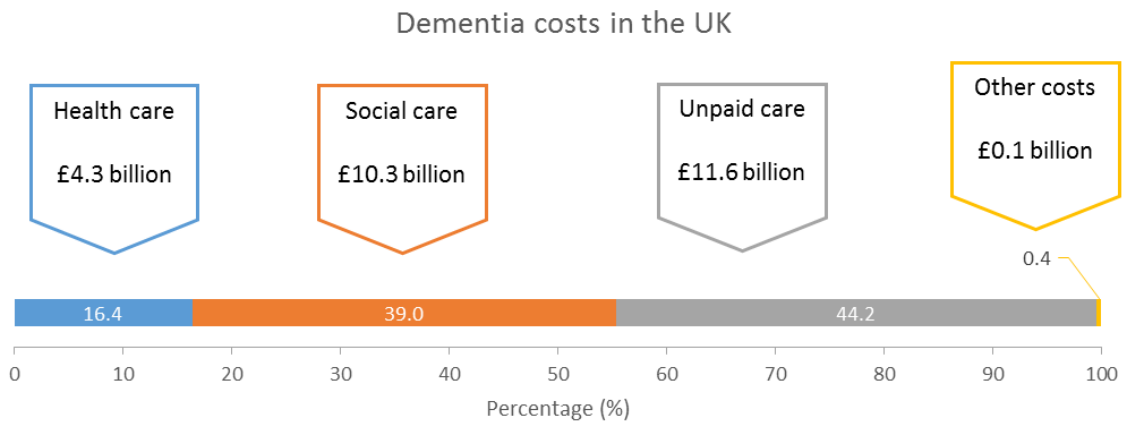


Studies on dementia incidence from the Netherlands [20], France [21], UK [6], USA [22, 23] and Nigeria [22] also overall suggest a stable or declining rate over time [9, 11]. Declining dementia prevalence and incidence could be explained by large societal changes between the birth years for first and second cohorts. The older generations included in these studies would have experienced war, with changes in life expectancy as well as living conditions and improvements in health care. Participation in higher education has increased at the same time as cardiovascular factors decreasing over time which would all contribute to changes in dementia incidence and prevalence.

Despite these positive changes the number of people with dementia is still expected to increase [24], this is because the older population aged 65 years and above will increase to a greater extent in the future. Currently there is limited evidence on whether numbers would still be expected to increase if dementia risk factor trends continue to improve as they have in recent decades.

In 2014 costs of dementia were estimated at £26.3 billion in the UK [2]. The largest proportion of which was estimated to be spent on unpaid care, accounting for £11.6 billion, 44.2% of costs associated with dementia (Figure 1.3) [2]. Health care costs for dementia come to £4.3 billion annually, 16.4% of total costs (Figure 1.3), covering primary, secondary and community care. Social care including costs related to public and private care management, residential care and home-based community care. A total of £10.3 billion, 39.0% of the total cost of dementia in a year was spent on social care. Other costs came to £0.1 billion a year, 0.4% of total yearly costs for police, research and advocacy and support costs. Costs of dementia are expected to rise in the future in the UK [25] and further afield [24, 26] but could be attenuated by a delay in dementia onset [27].

Figure 1.3: Percentage of dementia costs for different services. Data from [2].



Years of healthy life lost in a population due to morbidity and mortality from a health condition can be measured by disability adjusted life years (DALYs) [28]. Burden of dementia, measured by DALYs, is high and estimated to increase in the future [29]. Multi-morbidity (having two or more health conditions) in the future is also expected to increase in the future [4] and dementia often presents with comorbid health conditions [30]. Fewer people are now moving into care settings than before [7]. Those who do move have a higher prevalence of dementia and number of health conditions [1] whilst those who do not move and remain in the community rely more heavily on unpaid care than individuals with other long term health conditions [31].

For these reasons dementia is a priority when thinking of health and care needs in the future. There is currently no preventative or curative treatment for dementia. Given that changes in the brain occur years before symptoms present [32], treatments would have to reverse brain pathology or otherwise slow progression of dementia or mortality before any onset of symptoms or adverse event indicators. Without reversing the underlying pathology of dementia, these treatments could potentially increase the prevalence of dementia if survival is increased as older age is one of the largest risk factors for dementia. Therefore to reduce cases of dementia in the future, preventative strategies should be sought. This has been recognised by the World Health Organisation (WHO) whose global action plan on the public health response to dementia outlined dementia risk reduction as an action area [33].

1.3 Summary of dementia risk factor literature

Since dementia was identified as a public health priority by the World Health Organisation (WHO) [34] and at the G8 Dementia Summit [35], dementia risk has been a highly reviewed subject with many reviews covering a broad range of dementia risk factors. Causation can only be determined through randomised controlled trials, however, in most cases with dementia risk this is either not possible (health conditions) or unethical (smoking or alcohol intake). Therefore when looking at risk factors for dementia an assumption has to be made about the direction of the association. Sometimes results from other fields of research can help to determine the direction of association, for instance smoking and cancer, or withdrawal from exposure and reduction of the health condition after lengthy of follow up. To demonstrate the quantity of literature on the subject dementia risk a search was conducted for literature reviews published in the last five years and any reviews that covered multiple risk factors for dementia were identified and included in Table 1.1.

Table 1.1: Summary of reviews on multiple dementia risk factors.

Review	**Risk factors covered**	**Reported association with dementia**
2014 World Alzheimer Report [36]	Leg length and head circumference Stressful early-life events Education and Occupation Depression Anxiety Psychological distress Sleep Smoking Alcohol Physical activity Cognitive stimulation Diet Hypertension Obesity Cholesterol Diabetes	Education Occupation Later life depression Smoking Hypertension Diabetes
Barnes and Yaffe [37] (2011), updated by Norton et al. [38] (2014)	Diabetes Midlife hypertension Midlife obesity Physical inactivity Depression Smoking Low educational attainment	Diabetes Midlife hypertension Midlife obesity Physical inactivity Depression Smoking Low educational attainment

Review	Risk factors covered	Reported association with dementia
UK Health Forum [39] for Blackfriars consensus on brain health [40] (2014)	Alcohol Diet Physical activity Smoking Blood pressure Diabetes Obesity Cholesterol	Mediterranean diet Physical activity Smoking Diabetes Midlife obesity Midlife cholesterol
Imtiaz et al. [41] (2014)	Hypertension Cholesterol BMI Diabetes Education Physical activity Smoking and alcohol Dietary patterns Social characteristics Genetic risk factors	Midlife hypertension Cholesterol Midlife high BMI Diabetes Education Physical activity Smoking Alcohol Diet APOE ε4
Reitz and Mayeux [42] (2014)	Cerebrovascular disease Blood pressure Type 2 diabetes Body weight Plasma lipid levels Metabolic syndrome Smoking Traumatic brain injury Diet Physical activity Intellectual activity	Cerebrovascular disease Midlife hypertension Type 2 diabetes Body weight Metabolic syndrome Smoking Traumatic brain injury Mediterranean diet Intellectual activity
Di Marco et al. [43] (2014)	Lifestyle Work complexity Social activity Leisure activities Physical activity Cognitive engagement Tea and coffee consumption Smoking Alcohol Diet	Dietary fats Mediterranean diet Cognitively and socially engaging leisure activities Physical activity

Review	Risk factors covered	Reported association with dementia
Baumgart et al. [44] (2015)	Diabetes Midlife obesity Midlife hypertension Cholesterol Smoking Physical activity Diet Alcohol Cognitive training Social engagement Education Traumatic brain injury Depression Sleep	Diabetes Midlife obesity Smoking Physical activity Mediterranean diet Cognitive training Education Traumatic brain injury Depression Sleep
Deckers et al. [45] (2015)	Depression Diabetes Cognitive activity Physical activity Hypertension Diet Obesity Smoking Low/moderate alcohol High cholesterol Coronary heart disease Renal dysfunction Low unsaturated fat Inflammation	Depression Midlife hypertension Physical inactivity Diabetes Midlife obesity High cholesterol Smoking
Lafortune et al. [46] (2016)	(All midlife) Physical activity Diet and nutrition Smoking Alcohol Social activity Weight change/cycling	Midlife physical activity Midlife smoking
Livingston et al. [47] (2017)	Diabetes Midlife hypertension Midlife obesity Physical inactivity Depression Smoking Low educational attainment Hearing impairment Social isolation	Diabetes Midlife hypertension Midlife obesity Physical inactivity Depression Smoking Low educational attainment Hearing impairment Social isolation

Review	Risk factors covered	Reported association with dementia
Carroll and Turkheimer [48] (2018)	(All early to midlife) Education Occupation Personality Anxiety Depression Nicotine use Alcohol use BMI Physical activity Blood pressure Diabetes Cholesterol Social support	(All early to midlife) Education Occupation Anxiety Depression Smoking Alcohol Obesity Physical activity Hypertension Diabetes Cholesterol Social support

Possibly the most comprehensive review was the 2014 World Alzheimer Report [36] conducted by Alzheimer's Disease International on a vast number of risk factors at different points in the life course, concentrating on protective and modifiable factors. The report concluded that there was moderate to strong evidence for the associations between education, occupation, later life depression, smoking, hypertension and diabetes with dementia. High educational and occupational achievement were both considered protective factors for dementia whereas depression, smoking and diabetes were risk factors for dementia. The association between hypertension and dementia changed depending on the point in life where hypertension was measured. Midlife hypertension increased risk of dementia whilst later life hypertension decreased risk of dementia. Education and occupation were only considered as early to midlife factors. Diabetes and smoking increased risk of dementia whether measured at mid or later life. As later life depression was strongly associated with dementia but midlife depression was not, the direction of the association is unclear.

Reviews conducted around the same time period and since support these findings (Table 1.1) but in addition many name midlife obesity as a risk factor and physical activity as a protective factor for dementia. Diet, cholesterol, traumatic brain injury, alcohol intake, cerebrovascular disease, metabolic syndrome, cognitive activity, sleep, hearing impairment and social isolation were also reported as risk factors for dementia but with less or varying evidence. Some of these risk factors were included in the 2014 World Alzheimer's Report but had inconclusive evidence. This difference could be for several reasons. Reviews conducted in the same time period may have overlapping

references but due to different selection or inclusion criteria the evidence could lead to different conclusions. Another reason for differences in results could be that risk associated with dementia itself is changing over time for different risk factors. Changes in care, medication, lifestyles and earlier detection of risk factors will impact dementia risk. Due to changes in prevalence and incidence of dementia some studies have started assessing whether risk associated with dementia has changed over time [23, 49, 50]. This will be discussed further in Chapter 4.

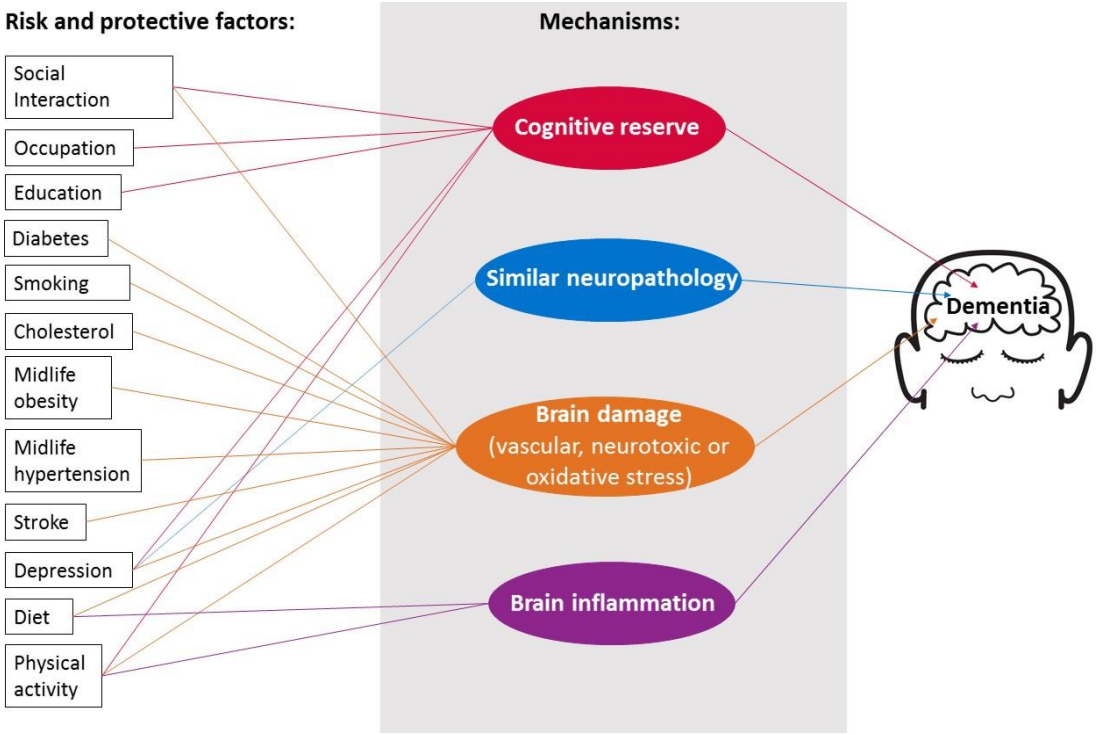
To be included in a review risk factor evidence has to be collated from many sources. Therefore these named risk factors may be biased towards risk factors that have been studied extensively. Deckers et al. [45] found reports of many more dementia risk factors that have been studied less intensely but could be of equal or higher importance, including demographic, health, lifestyle, environmental, genetic and other factors.

Since 2014 more research has been published on the association between obesity and dementia. Qizilbash et al. controversially found that midlife obesity decreased risk of dementia [51], however the measurement of obesity was in individuals aged 40 years or over. In a sensitivity analysis on individuals aged 55 years or less at first Body Mass Index (BMI) measurement with follow up of at least 15 years there was no association between obesity and dementia. This is in agreement with another study that shows that length of follow up is key to the association between obesity and dementia, with increased risk first showing after 20 years of follow up [52]. A recent meta-analysis and review also found no association between obesity and dementia in studies with follow up less than 20 years and that results from health record studies (such as [51]) were more heterogeneous than results from prospective cohort studies [53]. The majority of studies published have found increased risk of dementia from midlife obesity [52-59] or no association [60, 61] although Li et al. [60] grouped overweight and obese together. Knopman et al. [55] used a subset of the same data from Gottesman et al. [56] that included only those with full follow-up dementia assessment, Gottesman et al. only found an increased risk of dementia from obesity in white Americans. Studies since the 2014 World Alzheimer's report show that there is an association between obesity and dementia and that length of follow up is the key to this association. This is supported with evidence there is no association between being overweight or obese in later life and dementia [62].

Evidence for the association between midlife physical activity and dementia since 2014 has been more mixed. A study comparing physical activity trajectories in those with dementia to those without dementia found that physical activity was lower in the dementia group up to nine years before dementia onset [63]. Dementia diagnosis was through health record data and there was no association between midlife physical activity and dementia or cognitive function [63]. Others have either confirmed no association between midlife physical activity and dementia [60, 64, 65] or found an increased risk of dementia from low physical activity [66-69]. Another study found an association between midlife physical activity and cognitive impairment but the structure of the twin study was not taken into account, when looking at within twin variations there was no association between physical activity and cognitive impairment [70]. There is a possibility that the association between later life physical activity and dementia is because those with dementia become less active. The evidence on physical activity and dementia is still mixed and large meta-analyses such as [52, 53] for midlife obesity are needed to determine whether these differences are due to study design or length of follow up.

For a summary on mechanisms between risk and protective factors and dementia see Figure 1.4. The association between education and dementia could be explained by cognitive reserve where those with high cognitive reserve are able to compensate for dementia pathology [47]. Although dementia pathology occurs years before clinical symptoms present, 10% to 40% of individuals with mild to moderate dementia pathology in autopsy studies did not show dementia symptoms [71]. Therefore everyone who develops dementia pathology does not necessarily present with dementia symptoms [72] and one of the reasons for this could be cognitive reserve. Research has shown several biological markers that could indicate compensation [73]. High educational achievement, occupational achievement and social interaction are thought to increase cognitive reserve [74]. The mechanism linking depression and dementia is still unclear. Depression could result from dementia or be an indicator of the very early stages of dementia. If depression is a separate, independent risk factor for dementia this could be explained by the occurrence of underlying neuropathology associated with both (such as neuronal loss, ß-amyloid plaques and neurofibrillary tangles) [75], through increased risk of cerebrovascular disease [76] or by decreasing cognitive reserve [75]. Cerebrovascular disease provides the mechanism for many vascular diseases such as stroke, midlife obesity, midlife hypertension and diabetes [36].

Figure 1.4: Potential mechanisms between risk and protective factors and dementia, data from [36, 47]



As stated at the beginning of this chapter, in most cases it is not possible or ethical to conduct randomised controlled trials on risk factors for dementia. Therefore, when considering incident dementia risk, most evidence comes from longitudinal cohort studies. The purpose of cohort studies is to obtain findings that are generalizable to the population by using a sample that is population representative. Although a cohort study may begin as representative at baseline, this may deteriorate if those who remain in the study differ to those who die or drop-out. Many cohort studies still do not report on longitudinal attrition, despite its importance to the generalisability of results. A previous literature review found age and cognition to be the only consistent risk factors of attrition [77], another review suggests education and socioeconomic status are also consistent risk factors for attrition [78]. Given the association between education, socioeconomic status and cognition with attrition and with each other, it is important to control for this in analysis either through the use of inverse probability weighting [79] or multiple imputation [80].

1.4 Thesis aims and objectives

Although there has been much research into risk factors for dementia, especially in recent years, there are still gaps that this dissertation will aim to address:

a) Temporal changes in risk associated with dementia and prevalence of dementia risk factors

Changes to prevalence and incidence of dementia over time are likely to occur because of changes in dementia risk factors and their association with dementia. Many current studies have only considered dementia risk at one time point or have combined risk from several time points for a single estimate. Before analysing incident dementia risk, longitudinal attrition will be studied in each cohort.

b) Temporal changes to the proportion of incident dementia associated with individual risk factors

The Population Attributable Fraction (PAF) uses the prevalence of a risk factor and their association with dementia to measure the proportion of incident dementia cases associated with that particular risk factor. If the prevalence of dementia risk factors or risk associated with dementia changes over time it follows that the PAF will also be changing over time.

c) Future dementia trends

It is unclear whether dementia prevalence will continue to decline in the future as it has in recent decades due to population ageing. If current trends in dementia risk factors continue to improve, this could offset the influence of population ageing.

d) Lifelong education as an intervention

As education is strongly associated with cognitive reserve, the final aim is to investigate the potential of using later life education as an intervention for cognitive decline.

1.5 Thesis Structure

This thesis consists of eight chapters: an introduction Chapter 1, a description Chapter 2 of the main datasets used throughout this thesis, five chapters on original analysis (Chapters 3 – 7) and a summary Chapter 8. Chapters 2 through 7 can be split into four broad sections.

First Section: Data) Includes Chapters 2 and 3. Chapter 2 describes the main datasets used in the first part of the thesis, the Cognitive Function and Ageing Studies and Chapter 3 investigates longitudinal attrition between baseline interview and two year follow up interview in these studies.

Second Section: Epidemiology) Includes Chapter 4 on the prevalence of risk factors that may be associated with dementia and analysis of their association with incident dementia at two time points two decades apart.

Third Section: Primary dementia prevention) Includes Chapters 5 and 6. Both original analysis chapters exploring the proportion of incident dementia cases associated with individual risk factors (population attributable fractions, Chapter 5) and forecasting future dementia accounting for temporal trends in dementia risk factor prevalence and looking at how prevention of risk factors now could potentially impact future dementia (Chapter 6).

Fourth Section: Intervention) Includes Chapter 7 which consists of a systematic review on lifelong education and cognition and original analysis using the Cambridge Centre for Ageing and Neuroscience study on whether education in later life in addition to education in young adulthood is associated with cognition.

All chapters on original analysis include a brief background on the subject, methods, results, discussion and conclusions except Chapter 7 which additionally includes the systematic review followed by a description of the study used for original analysis and methods, results and discussion for the analysis and conclusions. All statistical analysis was carried out in Stata 14.

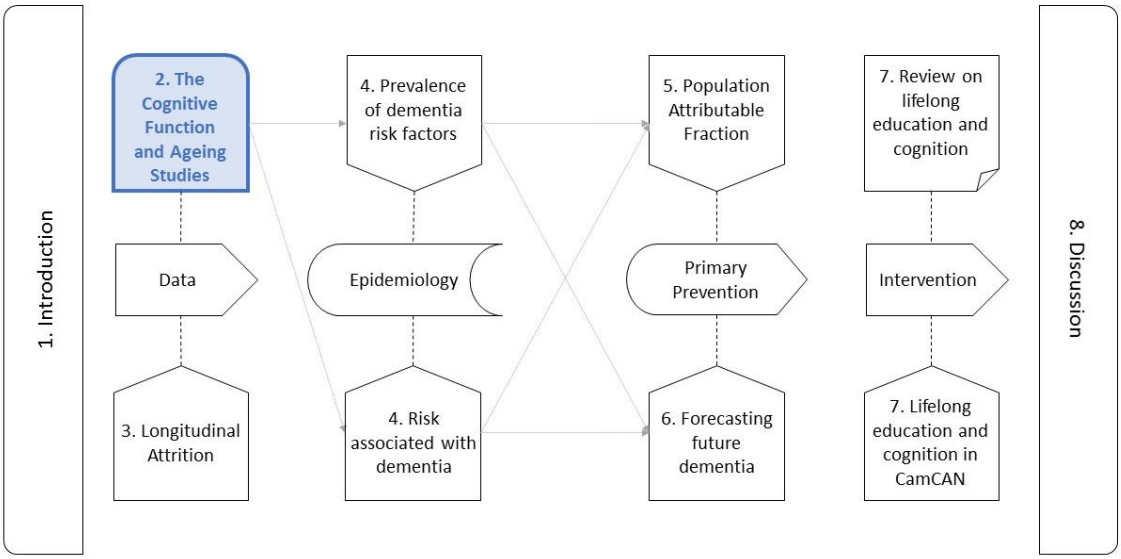
At the beginning of each chapter a figure will be included of the thesis structure with the current chapter highlighted.

Chapter 2: The Cognitive Function and Ageing Studies

2.1 Chapter overview

This chapter introduces the Cognitive Function and Ageing Studies, including the Medical Research Council Cognitive Function and Ageing Study (MRC CFAS), CFAS I (MRC CFAS data restricted to three centres) and CFAS II. MRC CFAS and CFAS II give individual level data on demographic, lifestyle and health factors with a focus on dementia and cognitive function. All are designed to be representative of the population aged 65 years and above. MRC CFAS ran from 1989 to 2011. CFAS II started in 2008 and is ongoing. The CFAS website has information on these studies [81].

Sections 2.2 and 2.4 give basic information on study design, sampling process and risk factor measurement for MRC CFAS and CFAS II respectively. Section 2.6.2 discusses the strengths and limitations of the Cognitive Function and Ageing Studies.



2.2 The Medical Research Council Cognitive Function and Ageing Study (MRC CFAS)

2.2.1 Study design and sampling process

MRC CFAS was originally conducted in six centres around the UK – Cambridgeshire, Newcastle, Nottingham, Oxford, Gwynedd and Liverpool (Figure 2.1). Cambridgeshire, Newcastle, Nottingham, Oxford and Gwynedd started in 1991 and followed the same study design. Liverpool had already started in 1989 with a different study design called the Ageing in Liverpool Project – Health Aspects (ALPHA) study. The areas were purposely chosen to be a mixture of rural and urban settings.

Individuals were randomly sampled from Family Health Service Authority lists – General Practice (GP) registers – in each defined centre. To estimate dementia prevalence and incidence accurately people living in care and nursing homes were included in the sampling frame. In each centre there was a sample size of 2500, stratified to have equal numbers in age groups 65-74 years and 75 years and above. The exception was Liverpool where the sample size was 5000 and was instead stratified by age and sex to have equal numbers in each five year age group.

Figure 2.1: Areas from the Medical Research Council Cognitive Function and Ageing Study. Source: [82]

GP surgeries were contacted with the list of sampled patients from their surgery and were asked to exclude anyone in the final stages of terminal illness or where there would be perceived risk to the study interviewer. An invitation was then sent to eligible individuals explaining the study with a photo of the interviewer who would visit them in the next seven days. When the interviewer visited they would explain the study further and individuals were given the chance to ask questions about participation. The participant could then set up a 90 minute interview if they wished or could decline at this point. This resulted in 13,004 consenting to take the baseline screening interview (S0) in MRC CFAS (Figure 2.2), a response rate of 80%. Interviews were conducted face to face in the participant's home and were computerised.

An informant interview was requested for a weighted subsample of the participants. Participants would nominate a family member, friend or carer for the informant interview and importantly for those who were potentially cognitively frail this could be used as an alternative source of information.

2.2.2 Interviews

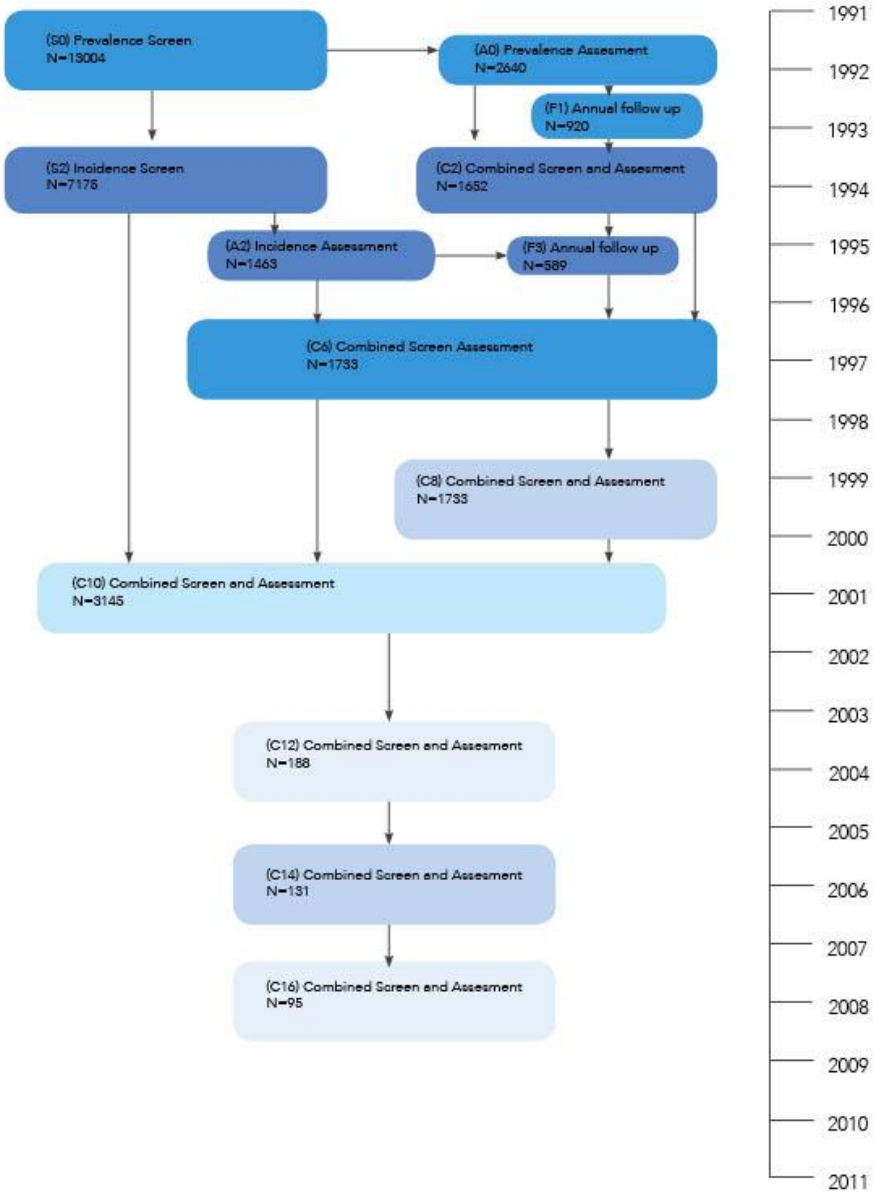
The screening interview consisted of questions on a variety of topics including but not limited to health, social contact, lifestyle, service use and medication use. Activities of Daily Living (ADL) and Instrumental Activities of Daily Living (IADL) were measured using questions from the modified Townsend scale [83]. Deprivation was measured by the Townsend deprivation index [84]. Cognitive function at the screening interview was assessed using the Mini Mental State Examination (MMSE - [85]).

A 20% sample of participants at baseline (N=2640) were asked to participate in a full study dementia assessment interview based on cognitive function (A0 – Figure 2.2). Those with an MMSE score of less than or equal to 21 or an incomplete MMSE score were asked to assessment. For further information on study dementia diagnosis see section 2.5.

Participants from Cambridgeshire, Newcastle, Nottingham, Oxford and Gwynedd were followed up over two decades from 1991 to 2011 (Figure 2.2). Those from the baseline screening interview (S0)

that did not participate in the dementia assessment (A0) were asked to participate in another screening interview two years later (S2, N=7175) and potentially then asked to go on to a dementia assessment interview (A2). Individuals who took part in the baseline dementia assessment (A0) were asked two years later, the same timing as S2 to participate in a combined interview (C2, N=1652) that involved screening and dementia assessment interview in one. At later stages all screening and assessment interviews were rolled into one.

Figure 2.2: MRC CFAS study design and interview. Source: [86]



2.3 CFAS I

CFAS I refers to data from MRC CFAS but restricted to only three centres. This restriction to centres Nottingham, Newcastle and Cambridgeshire allows comparison with CFAS II.

2.4 CFAS II

2.4.1 Study design and sampling process

CFAS II was designed to provide a temporal comparison of dementia prevalence and incidence with CFAS I and began in 2008. CFAS II randomly sampled 2500 individuals from each of three centres in Newcastle, Nottingham and Cambridgeshire.

The same sampling process was followed in CFAS II to MRC CFAS so that direct comparisons could be made. Individuals aged 65 years and above were randomly sampled from Primary Care Trusts (previously Family Health Service Authority), stratified by age groups 65-74 years and 75 years and over to have equal numbers in both groups. Out of those eligible 7796 individuals agreed to participate in the baseline interview (W1), a response rate of 56%. A weighted 20% subsample of participants nominated a family member, friend or carer for the informant interview. Information from the informant interview could be used as proxy information if the participant interview was not answered fully.

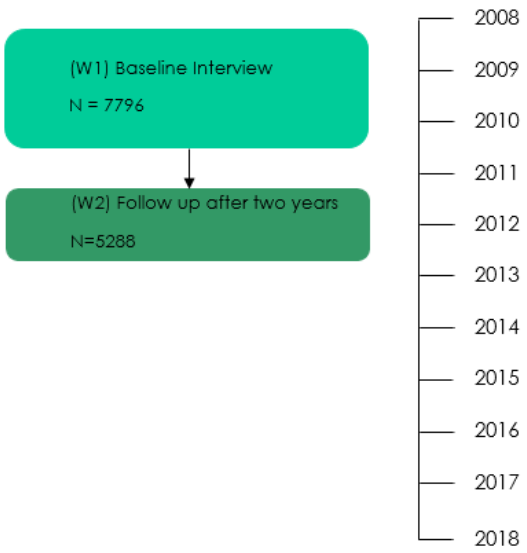
2.4.2 Interviews

The interviews for CFAS II covered the same topics as MRC CFAS, including the measurements for cognition and functional impairment. In addition, more information was available for, amongst other things, diet and exercise.

All interviews conducted to date in CFAS II have included a dementia assessment on everyone participating. Interviews were not split into screening and assessment as they were at the beginning of MRC CFAS. Dementia assessment was the same as in MRC CFAS so that direct comparisons could be made.

There are currently two waves of CFAS II with the follow up conducted two years after baseline (W2 – Figure 2.3). A subset of CFAS II participants are currently undergoing a 10 year interview.

Figure 2.3: CFAS II study design and interview



2.5 Study dementia diagnosis

Importantly, between MRC CFAS and CFAS II the study diagnosis of dementia was the same. Study diagnosis of dementia was given by the Geriatric Mental State Automated Geriatric Examination for Computer Assisted Taxonomy (GMS AGECAT) algorithm [87, 88]. The GMS AGECAT is a comprehensive mental health interview designed specifically for use with older people and can be used for diagnosis of dementia, depression, mania, schizophrenia and paranoia, obsessional, phobic, hypochondriacal and anxiety neuroses. Diagnosis of dementia through the GMS AGECAT has been validated against DSM IIIR criteria [87]. If information for the algorithm was not complete then a diagnostician (Carol Brayne) would review the participant and informant interviews and give a DSM IIIR diagnosis of dementia.

2.6 Dementia risk factor percentages and item non-response

Here the percentage of different dementia risk factors are given with percentage of item non-response as well. Overall percentages are given Tables 2.1 to 2.3, percentages by sex are given in Tables 2.4 to 2.6 and percentages by education level are given in Tables 2.7 to 2.9. These percentages are not inverse probability weighted as those with item non-response cannot be weighted. Therefore these results may not be population representative and are given here as a general description of these studies rather than as results for the population. Inverse probability weighted prevalence of risk factors overall are given in Chapter 4.

Questions from the CFAS interviews used to create the risk factor variables are in Appendix A1. Functional disability in ordinary and instrumental activities of daily living (ADL and IADL) was measured using the modified Townsend score [89]. Deprivation was measured by the Townsend deprivation scale [84] split into tertiles. Other risk factors in this analysis were: education (≤9, 10-11, ≥12), marital status (married, single or divorced, widowed), social class (skilled, semi-skilled, unskilled), self-perceived health (excellent, good, fair, poor), smoking (never, quit at least 5 years ago, present smokers and recent ex-smokers), alcohol intake (ever or never consumed an alcoholic drink during lifetime in CFAS I and 5+ days a week, 1-4 days a week, 1-4 times in 2 months, 0-2 times

a year in CFAS II), feelings of loneliness, reported friendships and frequency of visits from relatives were all self-reported. Health conditions were also self-reported and included: angina, peripheral vascular disease, heart attack, hypertension, hypotension, transient ischaemic attack, stroke, depression, fits/epilepsy, headaches, head injury, Parkinson's disease, meningitis, arthritis, breathing difficulties, diabetes, peptic ulcers, anaemia, shingles, thyroid, cancer, hearing difficulties, visual impairment and general anaesthetic. In CFAS I the Rose scale was used for peripheral vascular disease [90].

Table 2.1: Numbers, percentages and missingness in each category of demographic dementia risk factors in CFAS I and CFAS II

		CFAS I		CFAS II	
		n	%	n	%
Age Group (years)	65-69	1981	26.0	1939	25.0
	70-74	1776	23.3	1873	24.1
	75-79	1725	22.6	1624	20.9
	80-84	1308	17.1	1278	16.5
	85-89	615	8.1	737	9.5
	≥90	230	3.0	311	4.0
	Missing	0	0.0	0	0.0
Sex	Men	3045	39.9	3534	45.5
	Women	4590	60.1	4228	54.5
	Missing	0	0.0	0	0.0
Education	≤9	5529	72.4	2047	26.4
	10-11	1238	16.2	3923	50.5
	≥12	692	9.1	1667	21.5
	Missing	176	2.3	125	1.6
Social Class	Skilled	1960	25.7	1958	25.2
	Semi-skilled	3855	50.5	3962	51.0
	Unskilled	1579	20.7	1370	17.7
	Missing	241	3.2	472	6.1
Marital Status	Married	3766	49.3	4393	56.6
	Single	853	11.2	1005	13.0
	Widowed	2869	37.6	2332	29.9
	Missing	147	1.9	42	0.5
Place of residence	Community	6599	86.4	7083	91.3
	Semi-dependent housing	683	9.0	482	6.2
	Care settings	346	4.5	197	2.5
	Missing	7	0.1	0	0.0
Deprivation tertiles	Least deprived	2467	32.3	2576	33.2
	Mid-level deprivation	2419	31.7	2620	33.8
	Most deprived	2522	33.0	2566	33.1
	Missing	227	3.0	0	0.0

Table 2.2: Numbers, percentages and missingness of health condition dementia risk factors in CFAS I and CFAS II

		CFAS I		CFAS II	
		n	%	n	%
Vascular Disease	Angina	1011	13.2	1168	15.1
	Missing	63	0.8	151	2.0
	Peripheral Vascular Disease	320	4.2	784	10.1
	Missing	133	1.7	164	2.1
	Heart attack	761	10.0	832	10.7
	Missing	158	2.1	295	3.8
	Hypertension	2346	30.7	3943	50.8
	Missing	76	1.0	156	2.0
	Transient ischaemic attack	1203	15.8	681	8.8
	Missing	92	1.2	165	2.1
	Stroke	601	7.9	636	8.2
	Missing	64	0.8	154	2.0
Neurological Disease	Self-reported depression	884	11.6	579	7.5
	Missing	195	2.6	291	3.8
	Fits/epilepsy	156	2.0	164	2.1
	Missing	186	2.4	172	2.2
	Headaches	813	10.7	676	8.7
	Missing	198	2.6	1150	14.8
	Head injury	901	11.8	837	10.8
	Missing	187	2.5	354	4.6
	Parkinson's disease	78	1.0	71	0.9
	Missing	193	2.5	143	1.8
	Meningitis	64	0.8	154	2.0
	Missing	79	1.0	154	2.0
Other medical history	Arthritis	3988	52.2	4091	52.7
	Missing	148	1.9	140	1.8
	Breathing difficulties	1455	19.1	1465	18.9
	Missing	73	1.0	150	1.9
	Diabetes	471	6.2	1079	13.9
	Missing	64	0.8	143	1.8
	Peptic Ulcers	765	10.0	625	8.1
	Missing	189	2.5	180	2.3
	Anaemia	210	2.8	210	2.7
	Missing	72	0.9	147	1.9
	Shingles	1761	23.1	1761	22.7
	Missing	198	2.6	219	2.8
	Thyroid	438	5.7	696	9.0
	Missing	76	1.0	374	4.8
	Hearing Difficulties	1682	22.0	1981	25.5
	Missing	21	0.3	60	0.8
	Visual impairment	1007	13.2	1083	14.0
	Missing	38	0.5	113	1.5
	General Anaesthetic	3430	44.9	6055	78.0
	Missing	196	2.6	238	3.1

Age and sex in CFAS I and age, sex and place of residence in CFAS II were known for all individuals. In CFAS I missing data for risk factors ranged from 0.1% for place of residence (Table 2.1) to 7.6% for frequency of seeing relatives (Table 2.3). Loneliness was measured at the assessment interview so by design missing data had to exceed 80%, and was 82.4% (Table 2.3). In CFAS II missing data was between 0.5% for marital status (Table 2.1) and 14.8% for headaches (Table 2.2). Most risk factors in CFAS II had less than 5% missing data (Tables 2.1 – 2.3).

These descriptive statisticss should be interpreted with caution given that they are not inverse probability weighted but percentage of dementia risk factors differed between men and women in social class in CFAS II (Table 2.4), marital status in CFAS I and CFAS II (Table 2.4), place of residence in CFAS I (Table 2.4), heart attack in CFAS I and CFAS II (Table 2.5), self-reported depression in CFAS I and CFAS II (Table 2.5), head injury in CFAS I and CFAS II (Table 2.5), arthritis in CFAS I and CFAS II (Table 2.5), peptic ulcers in CFAS I and CFAS II (Table 2.5), thyroid problems in CFAS I and CFAS II (Table 2.5), functional impairment in CFAS I and CFAS II (Table 2.6), smoking in CFAS I and CFAS II (Table 2.6) and alcohol consumption in CFAS I and CFAS II (Table 2.6). Percentage of dementia risk factors differed between education level in social class in CFAS I and CFAS II (Table 7.7), marital status in CFAS II (Table 7.7), deprivation in CFAS I and CFAS II (Table 7.7), angina in CFAS II (Table 7.8), hypertension in CFAS II (Table 7.8), arthritis in CFAS II (Table 7.8), hearing difficulties in CFAS II (Table 7.8), general anaesthetic in CFAS I, self-perceived health in CFAS I and CFAS II (Table 7.9), functional impairment in CFAS II (Table 7.9), loneliness in CFAS II (Table 7.9), seeing relatives at least weekly in CFAS I and CFAS II (Table 7.9) and alcohol intake in CFAS II (Table 7.9).

Table 2.3: Numbers, percentages and missingness of other dementia risk factors in CFAS I and CFAS II

		CFAS I		CFAS II	
		n	%	n	%
Self-perceived Health	Excellent	1313	17.2	1484	19.1
	Good	3666	48.0	3812	49.1
	Fair	1944	25.5	1712	22.1
	Poor	494	6.5	427	5.5
	Missing	218	2.9	327	4.2
Functional Impairment	None	5236	68.6	4978	64.1
	Mild/moderate	1048	13.7	1498	19.3
	Severe	1267	16.6	1002	12.9
	Missing	84	1.1	284	3.7
Loneliness	Not lonely	1043	13.7	6220	80.1
	Lonely	303	4.0	1248	16.1
	Missing	6289	82.4	294	3.8
Friendships	Does not report friendships	1423	18.6	1126	14.5
	Reports friendships	6043	79.2	6541	84.3
	Missing	169	2.2	95	1.2
Meets relatives frequently	Less than weekly	1580	20.7	1657	21.4
	At least weekly	5475	71.7	5578	71.9
	Missing	580	7.6	527	6.8
Smoking	Never	2547	33.4	2909	37.5
	Past	3001	39.3	3598	46.4
	Current	1879	24.6	1037	13.4
	Missing	208	2.7	218	2.8
Alcohol intake	Ever	6639	87.0	NA	
	Never	782	10.2	NA	
	5 or more days a week	NA		1553	20.0
	1-4 days a week	NA		2215	28.5
	1-4 times in 2 months	NA		1243	16.0
	0-2 times a year	NA		2353	30.3
	Missing	214	2.8	398	5.1

Table 2.4: Numbers, percentages and missingness in each category of demographic dementia risk factors in CFAS I and CFAS II by sex

		CFAS I				CFAS II			
		Men		Women		Men		Women	
		n	%	n	%	n	%	n	%
Age Group (years)	65-69	915	30.1	1066	23.2	968	27.4	971	23.0
	70-74	780	25.6	996	21.7	902	25.5	971	23.0
	75-79	696	22.9	1029	22.4	758	21.5	866	20.5
	80-84	449	14.8	859	18.7	542	15.3	736	17.4
	85-89	167	5.5	448	9.8	278	7.9	459	10.9
	≥90	38	1.3	192	4.2	86	2.4	225	5.3
	Missing	0	0.0	0	0.0	0	0.0	0	0.0
Education	≤9	2235	73.4	3294	71.8	875	24.8	1172	27.7
	10-11	499	16.4	739	16.1	1843	52.2	2080	49.2
	≥12	266	8.7	426	9.3	779	22.0	888	21.0
	Missing	45	1.5	131	2.9	37	1.1	88	2.1
Social Class	Skilled	797	26.2	1163	25.3	1057	29.9	901	21.3
	Semi-skilled	1592	52.3	2263	49.3	1988	56.3	1974	46.7
	Unskilled	590	19.4	989	21.6	397	11.2	973	23.0
	Missing	66	2.2	175	3.8	92	2.6	380	9.0
Marital Status	Married	2126	69.8	1640	35.7	2536	71.8	1857	43.9
	Single	320	10.5	533	11.6	434	12.3	571	13.5
	Widowed	562	18.5	2307	50.3	547	15.5	1775	42.0
	Missing	37	1.2	110	2.4	17	0.5	25	0.6
Place of residence	Community	2753	90.4	3846	83.8	3299	93.4	3784	89.5
	Semi-dependent housing	208	6.8	475	10.4	180	5.1	302	7.1
	Care settings	82	2.7	264	5.8	55	1.6	142	3.4
	Missing	2	0.1	5	0.1	0	0.0	0	0.0
Deprivation tertiles	Least deprived	1041	34.2	1426	31.1	1203	34.0	1373	32.5
	Mid-level deprivation	946	31.1	1473	32.1	1177	33.3	1443	34.1
	Most deprived	980	32.2	1542	33.6	1154	32.7	1412	33.4
	Missing	78	2.6	149	3.3	0	0.0	0	0.0

Table 2.5: Numbers, percentages and missingness of health condition dementia risk factors in CFAS I and CFAS II by sex

		CFAS I				CFAS II			
		Men		Women		Men		Women	
		n	%	n	%	n	%	n	%
Vascular Disease	Angina	462	15.2	549	12.0	629	17.8	539	12.8
	Missing	10	0.3	53	1.2	49	1.4	102	2.4
	Peripheral Vascular Disease	168	5.5	152	3.3	391	11.1	393	9.3
	Missing	29	1.0	104	2.3	55	1.6	109	2.6
	Heart attack	420	13.8	341	7.4	544	15.4	288	6.8
	Missing	37	1.2	121	2.6	97	2.7	198	4.7
	Hypertension	856	28.1	1490	32.5	1768	50.0	2175	51.4
	Missing	16	0.5	60	1.3	49	1.4	107	2.5
	Transient ischaemic attack	504	16.6	699	15.2	335	9.5	346	8.2
	Missing	22	0.7	70	1.5	52	1.5	113	2.7
	Stroke	280	9.2	321	7.0	323	9.1	313	7.4
	Missing	12	0.4	52	1.1	47	1.3	107	2.5
Neurological Disease	Self-reported depression	223	7.3	661	14.4	174	4.9	405	9.6
	Missing	53	1.7	142	3.1	112	3.2	179	4.2
	Fits/epilepsy	63	2.1	93	2.0	59	1.7	105	2.5
	Missing	48	1.6	138	3.0	60	1.7	112	2.7
	Headaches	242	8.0	571	12.4	239	6.8	437	10.3
	Missing	53	1.7	145	3.2	436	12.3	714	16.9
	Head injury	547	18.0	354	7.7	536	15.2	301	7.1
	Missing	48	1.6	139	3.0	119	3.4	235	5.6
	Parkinson's disease	40	1.3	38	0.8	49	1.4	22	0.5
	Missing	50	1.6	143	3.1	46	1.3	97	2.3
	Meningitis	40	1.3	24	0.5	68	1.9	86	2.0
	Missing	16	0.5	63	1.4	51	1.4	103	2.4
Other medical history	Arthritis	1323	43.5	2665	58.1	1526	43.2	2565	60.7
	Missing	44	1.4	104	2.3	46	1.3	94	2.2
	Breathing difficulties	610	20.0	845	18.4	578	16.4	887	21.0
	Missing	15	0.5	58	1.3	48	1.4	102	2.4
	Diabetes	210	6.9	261	5.7	583	16.5	496	11.7
	Missing	13	0.4	51	1.1	46	1.3	97	2.3
	Peptic Ulcers	450	14.8	315	6.9	360	10.2	265	6.3
	Missing	49	1.6	140	3.1	63	1.8	117	2.8
	Anaemia	43	1.4	167	3.6	71	2.0	139	3.3
	Missing	18	0.6	54	1.2	47	1.3	100	2.4
	Shingles	645	21.2	1116	24.3	684	19.4	1077	25.5
	Missing	51	1.7	147	3.2	77	2.2	142	3.4
	Thyroid	51	1.7	387	8.4	129	3.7	567	13.4
	Missing	17	0.6	59	1.3	125	3.5	249	5.9
	Hearing Difficulties	725	23.8	957	20.9	986	27.9	995	23.5
	Missing	5	0.2	16	0.4	24	0.7	36	0.9
	Visual impairment	307	10.1	700	15.3	433	12.3	650	15.4
	Missing	3	0.1	35	0.8	38	1.1	75	1.8
	General Anaesthetic	1423	46.7	2007	43.7	2668	75.5	3387	80.1
	Missing	54	1.8	142	3.1	81	2.3	157	3.7

Table 2.6: Numbers, percentages and missingness of other dementia risk factors in CFAS I and CFAS II by sex

		CFAS I				CFAS II			
		Men		Women		Men		Women	
		n	%	n	%	n	%	n	%
Self-perceived Health	Excellent	568	18.7	745	16.2	767	21.7	717	17.0
	Good	1457	47.9	2209	48.1	1717	48.6	2095	49.6
	Fair	762	25.0	1182	25.8	728	20.6	984	23.3
	Poor	205	6.7	289	6.3	207	5.9	220	5.2
	Missing	53	1.7	165	3.6	115	3.3	212	5.0
Functional Impairment	None	2364	77.6	2872	62.6	2602	73.6	2376	56.2
	Mild/moderate	267	8.8	781	17.0	453	12.8	1045	24.7
	Severe	382	12.6	885	19.3	373	10.6	629	14.9
	Missing	32	1.1	52	1.1	106	3.0	178	4.2
Loneliness	Not lonely	411	13.5	632	13.8	3063	86.7	3157	74.7
	Lonely	87	2.9	216	4.7	378	10.7	870	20.6
	Missing	2547	83.7	3742	81.5	93	2.6	201	4.8
Friendships	Does not report friendships	580	19.1	843	18.4	543	15.4	583	13.8
	Reports friendships	2422	79.5	3621	78.9	2966	83.9	3575	84.6
	Missing	43	1.4	126	2.8	25	0.7	70	1.7
Meets relatives frequently	Less than weekly	724	23.8	856	18.7	853	24.1	804	19.0
	At least weekly	2100	69.0	3375	73.5	2442	69.1	3136	74.2
	Missing	221	7.3	359	7.8	239	6.8	288	6.8
Smoking	Never	401	13.2	2146	46.8	920	26.0	1989	47.0
	Past	1584	52.0	1417	30.9	2001	56.6	1597	37.8
	Current	1004	33.0	875	19.1	532	15.1	505	11.9
	Missing	56	1.8	152	3.3	81	2.3	137	3.2
Alcohol intake	Ever	2859	93.9	3780	82.4	NA			
	Never	129	4.2	653	14.2	NA			
	5 or more days a week					928	26.3	625	14.8
	1-4 days a week	NA				1245	35.2	970	22.9
	1-4 times in 2 months	NA				517	14.6	726	17.2
	0-2 times a year	NA				710	20.1	1643	38.9
	Missing	57	1.9	157	3.4	134	3.8	264	6.2

Table 2.7: Numbers, percentages and missingness in each category of demographic dementia risk factors in CFAS I and CFAS II by education level

		CFAS I						CFAS II					
		≤9 yrs educ		10-11 yrs educ		≥12 yrs educ		≤9 yrs educ		10-11 yrs educ		≥12 yrs educ	
		n	%	n	%	n	%	n	%	n	%	n	%
Age Group (years)	65-69	1450	26.2	355	28.7	161	23.3	87	4.3	1248	31.8	595	35.7
	70-74	1287	23.3	325	26.3	156	22.5	154	7.5	1297	33.1	404	24.2
	75-79	1275	23.1	259	20.9	170	24.6	515	25.2	788	20.1	304	18.2
	80-84	934	16.9	193	15.6	128	18.5	726	35.5	326	8.3	209	12.5
	85-89	417	7.5	85	6.9	63	9.1	404	19.7	186	4.7	110	6.6
	≥90	166	3.0	21	1.7	14	2.0	161	7.9	78	2.0	45	2.7
	Missing	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Sex	Men	2235	40.4	499	40.3	266	38.4	875	42.8	1843	47.0	779	46.7
	Women	3294	59.6	739	59.7	426	61.6	1172	57.3	2080	53.0	888	53.3
	Missing	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Social Class	Skilled	964	17.4	519	41.9	464	67.1	264	12.9	699	17.8	982	58.9
	Semi-skilled	3080	55.7	568	45.9	183	26.5	1078	52.7	2306	58.8	549	32.9
	Unskilled	1399	25.3	129	10.4	32	4.6	558	27.3	740	18.9	60	3.6
	Missing	86	1.6	22	1.8	13	1.9	147	7.2	178	4.5	76	4.6
Marital Status	Married	2726	49.3	675	54.5	344	49.7	861	42.1	2431	62.0	1075	64.5
	Single	583	10.5	148	12.0	114	16.5	226	11.0	515	13.1	242	14.5
	Widowed	2186	39.5	411	33.2	233	33.7	949	46.4	967	24.7	347	20.8
	Missing	34	0.6	4	0.3	1	0.1	11	0.5	10	0.3	3	0.2
Place of residence	Community	4804	86.9	1106	89.3	630	91.0	1737	84.9	3688	94.0	1578	94.7
	Semi-dependent housing	544	9.8	91	7.4	35	5.1	221	10.8	189	4.8	63	3.8
	Care settings	177	3.2	40	3.2	25	3.6	89	4.4	46	1.2	26	1.6
	Missing	4	0.1	1	0.1	2	0.3	0	0.0	0	0.0	0	0.0
Deprivation tertiles	Least deprived	1475	26.7	557	45.0	382	55.2	532	26.0	1252	31.9	760	45.6
	Mid-level deprivation	1751	31.7	410	33.1	207	29.9	651	31.8	1321	33.7	618	37.1
	Most deprived	2152	38.9	235	19.0	83	12.0	864	42.2	1350	34.4	289	17.3
	Missing	151	2.7	36	2.9	20	2.9	0	0.0	0	0.0	0	0.0

Table 2.8: Numbers, percentages and missingness of health condition dementia risk factors in CFAS I and CFAS II by education level

		CFAS I						CFAS II					
		≤9 yrs educ		10-11 yrs educ		≥12 yrs educ		≤9 yrs educ		10-11 yrs educ		≥12 yrs educ	
		n	%	n	%	n	%	n	%	n	%	n	%
Vascular Disease	Angina	774	14.0	158	12.8	73	10.6	400	19.5	579	14.8	179	10.7
	Missing	10	0.2	4	0.3	2	0.3	51	2.5	26	0.7	11	0.7
	Peripheral Vascular Disease	251	4.5	48	3.9	17	2.5	250	12.2	425	10.8	107	6.4
	Missing	59	1.1	10	0.8	11	1.6	54	2.6	29	0.7	14	0.8
	Heart attack	586	10.6	96	7.8	68	9.8	267	13.0	420	10.7	138	8.3
	Missing	38	0.7	10	0.8	3	0.4	112	5.5	73	1.9	28	1.7
	Hypertension	1746	31.6	377	30.5	204	29.5	1123	54.9	2028	51.7	762	45.7
	Missing	22	0.4	4	0.3	3	0.4	50	2.4	30	0.8	12	0.7
	Transient ischaemic attack	926	16.8	157	12.7	89	12.9	200	9.8	333	8.5	142	8.5
	Missing	28	0.5	6	0.5	5	0.7	53	2.6	36	0.9	14	0.8
	Stroke	453	8.2	67	5.4	47	6.8	225	11.0	296	7.6	101	6.1
	Missing	12	0.2	4	0.3	2	0.3	49	2.4	29	0.7	13	0.8
Neurological Disease	Self-reported depression	669	12.1	133	10.7	77	11.1	146	7.1	299	7.6	123	7.4
	Missing	55	1.0	11	0.9	3	0.4	78	3.8	108	2.8	34	2.0
	Fits/epilepsy	118	2.1	25	2.0	10	1.5	53	2.6	77	2.0	25	1.5
	Missing	48	0.9	11	0.9	3	0.4	63	3.1	35	0.9	15	0.9
	Headaches	643	11.6	114	9.2	50	7.2	177	8.7	392	10.0	105	6.3
	Missing	55	1.0	12	1.0	3	0.4	357	17.4	507	12.9	196	11.8
	Head injury	641	11.6	160	12.9	97	14.0	215	10.5	430	11.0	190	11.4
	Missing	48	0.9	12	1.0	3	0.4	141	6.9	93	2.4	31	1.9
	Parkinson's disease	58	1.1	10	0.8	8	1.2	23	1.1	34	0.9	10	0.6
	Missing	55	1.0	11	0.9	3	0.4	47	2.3	23	0.6	11	0.7
	Meningitis	55	1.0	7	0.6	2	0.3	37	1.8	83	2.1	33	2.0
	Missing	17	0.3	5	0.4	2	0.3	55	2.7	27	0.7	12	0.7
Other medical history	Arthritis	2939	53.2	650	52.5	359	51.9	1189	58.1	2086	53.2	769	46.1
	Missing	38	0.7	7	0.6	3	0.4	48	2.3	23	0.6	11	0.7
	Breathing difficulties	1123	20.3	197	15.9	110	15.9	406	19.8	750	19.1	298	17.9
	Missing	16	0.3	5	0.4	3	0.4	50	2.4	26	0.7	11	0.7

	CFAS I						CFAS II					
	≤9 yrs educ		10-11 yrs educ		≥12 yrs educ		≤9 yrs educ		10-11 yrs educ		≥12 yrs educ	
	n	%	n	%	n	%	n	%	n	%	n	%
Diabetes	347	6.3	74	6.0	39	5.6	317	15.5	552	14.1	199	11.9
Missing	14	0.3	5	0.4	2	0.3	47	2.3	23	0.6	11	0.7
Peptic Ulcers	566	10.2	135	10.9	63	9.1	186	9.1	336	8.6	100	6.0
Missing	51	0.9	11	0.9	3	0.4	67	3.3	36	0.9	16	1.0
Anaemia	161	2.9	32	2.6	14	2.0	87	4.3	94	2.4	28	1.7
Missing	19	0.3	5	0.4	2	0.3	51	2.5	23	0.6	11	0.7
Shingles	1271	23.0	306	24.7	177	25.6	498	24.3	883	22.5	374	22.4
Missing	58	1.1	11	0.9	3	0.4	84	4.1	47	1.2	19	1.1
Thyroid	301	5.4	91	7.4	39	5.6	225	11.0	354	9.0	116	7.0
Missing	21	0.4	5	0.4	2	0.3	148	7.2	101	2.6	35	2.1
Hearing Difficulties	1239	22.4	238	19.2	163	23.6	655	32.0	927	23.6	377	22.6
Missing	8	0.1	1	0.1	1	0.1	20	1.0	13	0.3	5	0.3
Visual impairment	754	13.6	149	12.0	85	12.3	380	18.6	490	12.5	198	11.9
Missing	9	0.2	1	0.1	1	0.1	36	1.8	17	0.4	7	0.4
General Anaesthetic	2391	43.2	620	50.1	402	58.1	1560	76.2	3116	79.4	1339	80.3
Missing	57	1.0	12	1.0	3	0.4	92	4.5	63	1.6	21	1.3

Table 2.9: Numbers, percentages and missingness of other dementia risk factors in CFAS I and CFAS II by education level

		CFAS I						CFAS II					
		≤9 yrs educ		*10-11 yrs educ*		*≥12 yrs educ*		*≤9 yrs educ*		*10-11 yrs educ*		*≥12 yrs educ*	
		n	%	n	%	n	%	n	%	n	%	n	%
Self-perceived Health	Excellent	873	15.8	259	20.9	174	25.1	304	14.9	755	19.3	403	24.2
	Good	2645	47.8	633	51.1	370	53.5	921	45.0	1965	50.1	901	54.1
	Fair	1546	28.0	265	21.4	119	17.2	558	27.3	867	22.1	270	16.2
	Poor	398	7.2	68	5.5	24	3.5	127	6.2	237	6.0	58	3.5
	Missing	67	1.2	13	1.1	5	0.7	137	6.7	99	2.5	35	2.1
Functional Impairment	None	3780	68.4	933	75.4	509	73.6	956	46.7	2752	70.2	1256	75.3
	Mild/moderate	789	14.3	155	12.5	99	14.3	543	26.5	701	17.9	249	14.9
	Severe	913	16.5	139	11.2	82	11.9	434	21.2	403	10.3	138	8.3
	Missing	47	0.9	11	0.9	2	0.3	114	5.6	67	1.7	24	1.4
Loneliness	Not lonely	775	14.0	152	12.3	69	10.0	1511	73.8	3269	83.3	1413	84.8
	Lonely	243	4.4	30	2.4	16	2.3	428	20.9	580	14.8	228	13.7
	Missing	4511	81.6	1056	85.3	607	87.7	108	5.3	74	1.9	26	1.6
Friendships	Does not report friendships	1125	20.4	198	16.0	80	11.6	370	18.1	543	13.8	183	11.0
	Reports friendships	4365	79.0	1031	83.3	609	88.0	1653	80.8	3370	85.9	1477	88.6
	Missing	39	0.7	9	0.7	3	0.4	24	1.2	10	0.3	7	0.4
Meets relatives frequently	Less than weekly	1001	18.1	335	27.1	225	32.5	359	17.5	773	19.7	509	30.5
	At least weekly	4245	76.8	814	65.8	384	55.5	1558	76.1	2970	75.7	1005	60.3
	Missing	283	5.1	89	7.2	83	12.0	130	6.4	180	4.6	153	9.2
Smoking	Never	1871	33.8	415	33.5	234	33.8	705	34.4	1414	36.0	736	44.2
	Past	2109	38.1	548	44.3	324	46.8	995	48.6	1816	46.3	754	45.2
	Current	1480	26.8	263	21.2	131	18.9	250	12.2	623	15.9	155	9.3
	Missing	69	1.3	12	1.0	3	0.4	97	4.7	70	1.8	22	1.3
Alcohol intake	Ever	4849	87.7	1111	89.7	642	92.8	NA					
	Never	607	11.0	115	9.3	47	6.8	NA					
	5 or more days a week	NA						326	15.9	723	18.4	502	30.1
	1-4 days a week	NA						442	21.6	1278	32.6	489	29.3
	1-4 times in 2 months	NA						303	14.8	659	16.8	278	16.7
	0-2 times a year	NA						817	39.9	1154	29.4	360	21.6
	Missing	73	1.3	12	1.0	3	0.4	159	7.8	109	2.8	38	2.3

2.7 Discussion

MRC CFAS and CFAS II are population based cohort studies that randomly sampled to be population representative of people aged 65 years and above living in the UK. Both included urban and rural areas and care and nursing homes were included in the sampling frame. Interviews included many questions on health, social contact, lifestyle, service use, medication use, functional impairment and cognitive function. The study diagnosis of dementia using the GMS AGECAT algorithm was the same in both studies and the same diagnostician (Carol Brayne) gave a DSM-IIIR diagnosis of dementia if full information for the GMS AGECAT was not available.

A discussion follows on CFAS I and CFAS II, including the differences between the two studies and their strengths and limitations.

2.7.1 Similarities and differences between CFAS I and CFAS II

CFAS I and CFAS II had the same population sampling process. Study design was similar but in CFAS I there was a two phase baseline interview that included a screening and an assessment whereas in CFAS II screening and assessment were combined in the baseline interview. Response rate in CFAS I and CFAS II also differed. In CFAS I response rate was 80% and in CFAS II response rate was 56%. This has been reported on previously [91] and will be discussed in the next section. Response rate for study diagnosis of dementia in CFAS I differed to initial response due to the two-stage design. Response rate to A0 in CFAS I was 74%, multiplying by the baseline response rate gives 59% response for dementia diagnosis in CFAS I, similar to the CFAS II dementia diagnosis response rate. CFAS I followed up participants over a period of two decades with interviews conducted every two years. Longitudinally CFAS I has more data than CFAS II. CFAS II has only one follow up wave conducted two years after baseline.

2.7.2 Strengths and limitations of the Cognitive Function and Ageing Studies

CFAS I and CFAS II are representative of the population aged 65 years and over in the UK. This means that risk estimates from the studies can be applied to the population as a whole. When thinking about population level interventions it is important to consider everyone in the population rather than only subgroups. Many risk factors are co-dependent so the broad range of risk factors covered in these studies means that risk estimates can be properly controlled for confounders.

Study diagnosis of dementia remained the same between CFAS I and CFAS II. This is especially important for comparisons given that the clinical diagnosis of dementia has changed over time. Research from other studies has shown that a changing diagnosis of dementia impacts on trends seen over time [21] so if the diagnosis in the two studies differed a direct comparison could not be made.

Stable sampling methods and study diagnosis of dementia mean that any changes between the two studies will be due to genuine differences in risk over time rather than because dementia diagnosis criteria or sampling design have changed.

Response rate was lower in CFAS II compared to CFAS I. Estimates would not be generalizable to the population if people who participate differ to those who do not. Difficulties arise when trying to analyse differences between responders and non-responders. Detailed factors associated with initial non-response cannot be investigated as limited information is available on people who do not participate in the study (age, sex, area deprivation). Previous analysis of CFAS I and CFAS II shows that non-response was associated with centre, being a woman and deprivation, but age was not associated with non-response in either study [91]. Methods such as inverse probability weighting can be applied to ensure population representativeness of results in these areas. Other studies have also reported decreasing participation over time [92-94]. Large changes in the data would have to occur for it to impact results [7].

Many of the risk factors are self-reported, public ideology could prevent people from answering truthfully with respect to items such as alcohol consumption, smoking and exercise. Self-report is also limited by memory. Informant interviews were undertaken in CFAS I and CFAS II asking the same as the participant questionnaire. Proxy report on health conditions agrees with self-reported health conditions [95]. This helps to ensure reliability in participant responses and for those who are cognitively impaired proxy information can be substituted from the informant interview.

Some restrictions to the analysis of dementia risk factors in the CFAS cohorts include length of follow up and not being able to investigate midlife risk factors. Different risk factors could be important depending on length of follow up. As CFAS II only has two waves of interviews, comparison between CFAS I and CFAS II is limited to two years of follow up longitudinally, and would therefore be short term risk factors. As an example cardiovascular health conditions are increasingly now thought to be more important in midlife than in late life but CFAS I and CFAS II both sample from the 65 years and over population and therefore do not have follow up from midlife. However, with prevention in mind, short term solutions when people reach the age of 65 years could potentially be the most helpful.

2.7.3 CFAS dementia risk studies

MRC CFAS has been used to estimate risk of dementia, using inverse probability weights to account for the two-stage dementia assessment design [96]. Incident dementia risk was estimated after two and six years separately and together. Older age, fair and poor self-perceived health, stroke and Parkinson's disease were associated with increased incident dementia risk after two years. Past smoking was associated with decreased dementia risk. The association between smoking and incident dementia is discussed further in Chapter 4. Older age, being female and poor self-perceived health were associated with increased risk of dementia after six years whereas higher education, general anaesthesia and shingles were associated with lower risk of dementia after six years.

Risk and protective factors for cognitive impairment were also explored in MRC CFAS. Higher education was associated with decreased risk of mild cognitive impairment [97], decreased risk of overall cognition [98] and with smaller reductions in cognition with age [99]. Having a more complex occupation was associated with decreased risk of mild cognitive impairment [97], decreased risk of overall cognition [98] and smaller reductions in cognitive decline with age [99]. Being more socially engaged was associated with decreased risk of transitioning from mild cognitive impairment to moderate/severe cognitive impairment [97]. Active cognitive lifestyle, a composite measure of education, occupation and social engagement was associated with decreased risk of mild cognitive impairment [100] and dementia [74]. Excellent self-perceived health was associated with decreased risk of cognitive impairment [101]. Taking a nap was associated with decreased risk of cognitive decline [102]. If land use in the area you reside is highly diverse this is associated with decreased risk of cognitive impairment [103, 104]. Area deprivation was associated with increased risk of cognitive impairment [98]. For those with cognitive impairment already, wandering and persecution psychological symptoms were associated with progression to dementia [105].

Cross-sectional analysis of CFAS II found that mood disorders were associated with cognitive impairment and that there was an interaction between cognitive lifestyle and mood disorders with smaller decreases in cognition for those with mood disorders in middle and high cognitive lifestyle groups in comparison to the low cognitive lifestyle group [106].

Work using CFAS Wales only (for more information on CFAS Wales see [107]) has shown there is a cross-sectional association between cognitive function and physical activity, alcohol intake, diet and cognitive and social activity [108]. There was a cross-sectional and longitudinal association between social isolation, measured using the Lubben Social Network Scale-6 [109], and cognitive function in CFAS Wales [110].

2.7.4 Conclusions

This chapter introduced the two main datasets used in this thesis, CFAS I and CFAS II. Both are representative of the population aged 65 years or above living in the UK. Although there are some

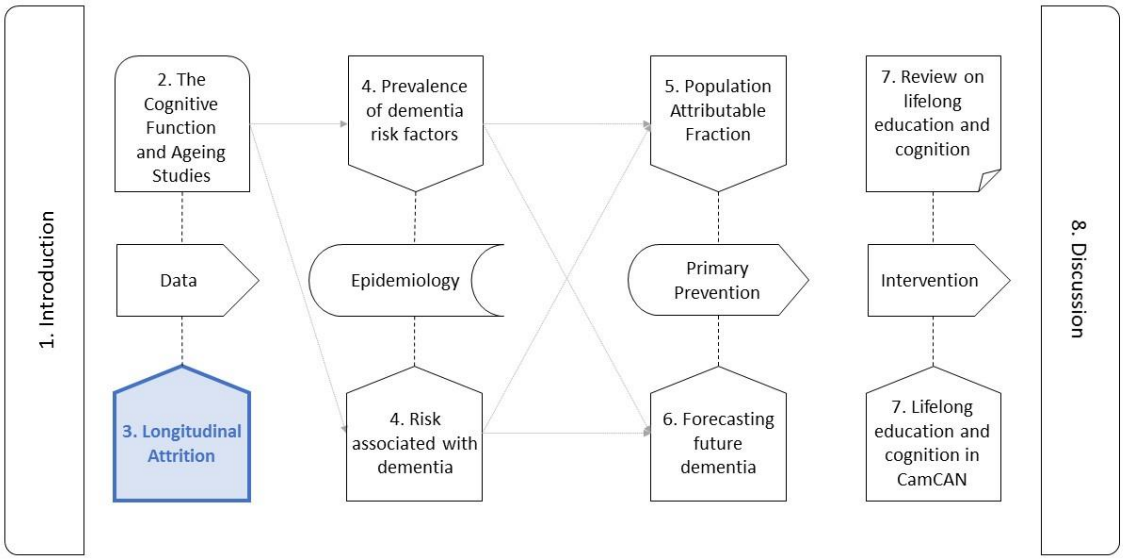
differences in study design they can be used to compare risk of dementia over time. The interviews covered a broad range of variables for dementia that would allow many risk factors to be investigated whilst being able to control for confounding. The literature on incident dementia risk from MRC CFAS, CFAS II and CFAS Wales demonstrates the diverse range of measures included in MRC CFAS. A strength to CFAS is that participants have been followed over many years, allowing comparison of risk and protective factors depending on length of follow-up.

Chapter 3: Attrition in the Cognitive Function and Ageing studies

3.1 Chapter overview

Before using wave two of CFAS II for risk factor analysis attrition between baseline and wave two needs to be established. If there are any differences between people who participate with further interviews compared to people who drop out then this needs to be accounted for in future analysis.

Attrition in MRC CFAS has been fully reported previously [111]. Here CFAS I will be analysed using the same methods as in CFAS II, to ensure that comparison with CFAS II is possible.



3.2 Background

Factors associated with attrition have long been known to have an impact on the generalizability of the results and conclusions from longitudinal studies [77, 112]. An earlier systematic review reported that when adjusted for other factors only age and cognition were consistently associated with longitudinal attrition [77]. Since then a number of longitudinal studies have described their longitudinal attrition patterns for both young old and in the oldest old and over short and longer term longitudinal follow-up [113-119]. Some new risk factors from multivariable analyses have been suggested, including home ownership, occupation and social class, living in a rural or less developed area and being single [113, 114, 116]. Some factors associated with attrition also appear to have remained fairly stable in each of these investigations for instance gender, age, education and social class [113, 115, 118-121], but not all studies find these associations [122]. Each of these studies has been undertaken in different settings with different methods and clear conclusions about whether factors associated with attrition are changing temporally cannot be stated.

As discussed in Chapter 2, initial non-response in CFAS II was markedly higher than CFAS I [91]. Longitudinal attrition is different to non-response as choosing to continue participation in a study is different to initially committing to take part. Without detailed investigation on attrition it is difficult to draw conclusions about the impact of response on estimates of diseases of interest.

Many analytical approaches are now available for the analysis of data with longitudinal dropout such as multiple imputation [80] and inverse probability weighting [79]. Both methods require knowledge of the factors associated with attrition to either understand the imputation model needed or to calculate appropriate weights. Attrition due to death is a different process. Investigations of results that impute past death creating a so called immortal cohort are to be used with caution [112], however factors associated with attrition due to death may be different to factors associated with longitudinal non-response and the impact of these factors on mortality may also have changed.

The aim of this analysis is to explore the factors associated with longitudinal attrition either due to death or refusal and see whether they have changed in populations sampled from the same geographical areas across 20 years.

3.2 Method

CFAS II details of baseline wave non-response, content of the interviews and sampling design have already been published [7, 91]. In both studies individuals were sampled from local GP lists for individuals aged 65 years and above from three sites in England – Cambridgeshire, Newcastle and Nottingham. Trained interviewers would visit respondents in their own home and undertake a structured, computer assisted interview. The baseline interview included basic demographics, information on functional impairment (ADL and IADL, the Townsend activities of daily living score [83]), socio-economic factors, health conditions and other health related outcomes, for instance self-perceived health, self-reported depression, loneliness, friendships, smoking and alcohol intake (measured as ever/never in CFAS I). The Geriatric Mental State Automated Geriatric Examination for Computer Assisted Taxonomy (GMS AGECAT [88, 123]) was used to give a study diagnosis of dementia (in 20% subsample in CFAS I, all in CFAS II) and other tests of cognition were also included, for example the Mini Mental State Examination (MMSE [85]). Importantly for the potentially frail population, informant interviews were also requested on a 20% subsample of individuals weighted to the cognitively and physically frail (in both studies).

All respondents who were interviewed (apart from those with just an informant) at the baseline interview were approached again two years later for wave 2 of the study. Individuals were classified as either having completed the interview successfully or if not, the reason for not participating was ascertained (e.g. refusal/moved/non-contact). If an individual refused to be interviewed they were not contacted again unless they had stated that the interview was 'not convenient' at present. Attrition between waves could also be due to death, all individuals who died have been traced for exact date and cause of death.

Factors potentially thought to impact on longitudinal attrition or death were defined from the baseline sample, with full details of the measures described elsewhere [124]. This included gender; age; place of residence including community, semi dependent housing or care settings; deprivation, using tertiles from the Townsend Deprivation Index [84]; social class as skilled, semi-skilled or unskilled; marital status as married, single/divorced and widowed; dementia; cognition measured by Mini Mental State Examination (MMSE); years of full time education split into ≤9, 10-11, ≥12 years; functional impairment split into none, mild/moderate and severe using ADLs and IADLs; number of self-reported health conditions (angina, peripheral vascular disease, hypertension, diabetes, Parkinson's disease, stroke, heart attack, epilepsy/fits, breathing difficulties, arthritis, headache, peptic ulcers, anaemia, transient ischaemic attack, current thyroid problems, hearing difficulties, visual impairment, meningitis and shingles) grouped as 0, 1, 2, and 3+; self-perceived health grouped as excellent, good, fair and poor; self-reported diagnosis of depression, feelings of loneliness, reported friendships, smoking either as a current smoker, past smoker (lagged by 5 years), or never smoked; and alcohol intake for ever or never during life in CFAS I and in CFAS II on a scale from drinking five or more days a week down to zero to two times a year. Separate logistic regression models were undertaken to investigate death and longitudinal drop out as different mechanisms would be expected and these factors may have changed differentially over time. Factors were investigated univariately, then adjusted for age and then fully adjusted for each other. A final model included all factors found to be associated with attrition at a $p<0.05$ or where the estimate of attrition/death was an odds ratio ≤0.7 or ≥1.4 giving adjusted odds ratios and 95% confidence intervals for all factors adjusted with each other, in either study. All models were weighted using inverse probability weights for sampling design and non-response at baseline [7]. This method adjusts for the oversampling of those aged 75 and above at baseline, and factors associated with initial non-response (age, gender and area deprivation).

3.3 Results

In CFAS I there were 7635 individuals at baseline of whom 819 died before the second interview and out of the 6816 still alive, 5156 (76%) participated in the two-year follow up interview with 1660 having either moved or refused the second interview. Out of the 7762 individuals seen in

the baseline wave of CFAS II, 645 had died before the two year follow-up interview. Of the 7117 still alive and available for approach 5288 (73%) participants took part in the interview and 1831 refused or moved away. Table 3.1 provides baseline characteristics of those interviewed at the second wave or who were lost to follow up or died between the first and second wave in CFAS II. There were differences in the baseline characteristics of people who were interviewed at wave two, those who were lost between waves and those who died between waves in age, place of residence, deprivation, education, marital status, functional impairment, dementia, cognitive impairment, number of health conditions, loneliness and alcohol consumption.

Table 3.1: Baseline characteristics by status of wave two inclusion in CFAS II

Factor		Interviewed (n=5288)		Died (n=645)		Lost (n=1829)	
		n	%	n	%	n	%
Sex	Women	2806	54.3	349	58.4	1073	60.1
Age (years)	65 – 69	1479	26.2	52	6.6	408	20.8
	70 – 74	1369	24.7	75	10.1	429	22.4
	75 – 79	1122	21.1	96	13.2	406	21.7
	80 – 84	803	16.2	160	24.3	315	18.1
	85 – 89	399	8.6	143	21.5	195	11.5
	90+	116	3.3	117	24.3	78	5.5
Place of residence	Community	4959	92.4	485	72.8	1639	88.3
	Semi-dependent housing	284	6.3	69	12.0	129	7.8
	Care settings	45	1.3	89	15.2	63	3.9
Deprivation	Least deprived	1873	31.2	166	22.3	537	25.5
	Middle deprived	1809	32.7	207	31.8	604	30.8
	Most deprived	1606	36.1	270	45.9	690	43.7
Social Class	Skilled	1491	27.6	124	23.0	343	19.7
	Semi-skilled	2761	54.3	286	53.3	915	54.7
	Unskilled	851	18.0	120	23.7	399	25.6
Education (years)	≤9	1182	24.9	293	50.5	570	33.9
	10 – 11	2769	52.0	225	34.7	931	51.1
	≥12	1288	23.1	94	14.7	285	15.0
Marital status	Married	3151	56.9	251	36.4	991	51.5
	Single/divorced	683	13.6	74	11.8	248	14.7
	Widowed	1442	29.6	302	51.8	578	33.8
Functional Impairment	None	3758	69.5	155	24.7	1065	59.7
	Mild/Moderate	1008	20.4	120	21.7	370	22.7
	Severe	466	10.1	279	53.6	257	17.6
Dementia		105	2.3	166	29.0	190	12.2
MMSE Score	0 – 17	76	1.8	69	13.6	68	4.8
	18 – 21	161	3.4	69	13.9	116	7.2
	22 – 25	758	15.2	134	24.9	397	24.1
	26 – 30	4251	79.7	280	47.7	1128	63.9
Number of Comorbidities	0	454	8.3	43	6.7	156	8.4
	1	937	17.1	78	12.0	306	16.3
	2	1210	22.6	105	15.3	384	21.0
	3+	2677	52.1	405	65.9	956	54.4
Self-perceived health	Excellent	1116	20.7	61	12.0	307	18.1
	Good	2763	52.3	215	41.9	834	48.8
	Fair	1117	22.2	163	30.0	432	26.8
	Poor	239	4.8	87	16.2	101	6.4
Self-reported depression	Depressed	386	7.5	45	8.1	148	9.0
Loneliness	Lonely	808	16.3	143	27.3	297	18.5
Friendships	Has friends	4587	86.7	465	76.4	1489	82.1
Smoking	Never	2050	38.8	160	31.9	629	37.7
	Past	2513	48.2	263	51.3	754	44.9
	Current	654	13.0	90	16.7	280	17.5
Alcohol intake	5 or more days a week	1151	21.5	94	18.0	308	18.0
	1 – 4 days a week	1665	31.5	104	20.1	446	26.2
	1 – 4 times every 2 months	896	17.1	80	14.6	267	15.9
	0 – 2 times a year	1492	29.9	225	47.3	636	40.0

3.3.1 Mortality

In the CFAS II univariate models mortality was associated with all factors except self-reported depression (Table 3.2). The strongest risk factor for mortality was age, followed by dementia, living in care settings and severe functional impairment. After adjusting for age the factors remained associated with mortality apart from sex.

The multivariable model that included all variables in Table 3.2 highlighted increased risk of mortality from being male, older age, living in care settings, functional impairment, dementia, cognitive impairment, poor self-perceived health, loneliness and current smoking. The association between sex and mortality is reversed after adjustment for age.

Estimates in Table 3.3 are adjusted for all variables included in the table after best fit models in CFAS I and CFAS II indicated the most important variables to include. Most results are similar between the two studies. Being a man, older age, living in care settings, mild/moderate or severe functional impairment, cognitive impairment or dementia, poor self-perceived health and currently smoking increased risk of mortality in both studies. In CFAS I there was no association between education and mortality but in CFAS II, further years in education was associated with reduced risk of mortality.

Table 3.2: Attrition due to death in CFAS II

N = 645 total died			Unadjusted		Age adjusted		Multivariable	
Factor		**n**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
Sex	Women	349	1.2	1.0 – 1.4	0.9	0.7 – 1.1	0.7	0.5 – 0.8
Age (years)	65 – 69	52	1	-	1	-	1	-
	70 – 74	75	1.6	1.1 – 2.4	1.6	1.1 – 2.4	1.5	1.0 – 2.3
	75 – 79	96	2.5	1.7 – 3.5	2.5	1.8 – 3.6	1.9	1.2 – 2.8
	80 – 84	160	5.9	4.2 – 8.3	5.9	4.2 – 8.3	3.0	2.0 – 4.7
	85 – 89	143	9.9	7.0 – 14.0	9.9	7.0 – 14.0	4.7	2.9 – 7.7
	90+	117	29.6	19.9 – 43.9	29.6	19.9 – 43.9	8.0	4.6 – 13.9
Place of Residence	Community	485	1	-	1	-	1	-
	Semi-dependent Housing	69	2.4	1.8 – 3.3	1.3	1.0 – 1.8	1.0	0.7 – 1.4
	Care settings	89	15.0	10.2 – 22.1	6.4	4.1 – 10.0	1.7	0.8 – 3.5
Deprivation	Least deprived	166	0.7	0.6 – 0.9	0.8	0.6 – 1.0	0.9	0.7 – 1.2
	Middle deprived	207	1	-	1	-	1	-
	Most deprived	270	1.3	1.1 – 1.6	1.3	1.0 – 1.6	1.1	0.8 – 1.5
Social class	Skilled	124	0.9	0.7 – 1.1	0.9	0.7 – 1.2	1.2	0.9 – 1.6
	Semi-skilled	286	1	-	1	-	1	-
	Unskilled	120	1.3	1.1 – 1.7	1.2	1.0 – 1.6	1.0	0.7 – 1.3
Education (years)	≤9	293	1	-	1	-	1	-
	10 – 11	225	0.3	0.3 – 0.4	0.7	0.6 – 0.9	0.8	0.6 – 1.1
	≥12	94	0.3	0.2 – 0.4	0.6	0.5 – 0.8	0.8	0.5 – 1.1
Marital Status	Married	251	1	-	1	-	1	-
	Single/divorced	74	1.4	1.0 – 1.8	1.2	0.9 – 1.7	1.0	0.7 – 1.4
	Widowed	302	2.7	2.3 – 3.3	1.2	1.0 – 1.5	1.1	0.8 – 1.4
Functional Impairment	None	155	1	-	1	-	1	-
	Mild/Moderate	120	3.0	2.3 – 3.8	2.0	1.5 – 2.6	1.6	1.1 – 2.1
	Severe	279	14.9	11.9 – 18.6	8.4	6.6 – 10.7	4.0	2.9 – 5.5
Dementia	Dementia	166	17.2	12.9 – 22.9	9.1	6.6 – 12.5	2.7	1.6 – 4.8
MMSE	0 – 17	69	12.8	8.9 – 18.4	6.5	4.3 – 9.8	0.8	0.4 – 1.7
	18 – 21	69	6.9	5.0 – 9.5	3.8	2.7 – 5.3	1.6	1.0 – 2.5
	22 – 25	134	2.7	2.2 – 3.4	1.9	1.5 – 2.4	1.3	0.9 – 1.7
	26 – 30	280	1	-	1	-	1	-
Number of Comorbidities	0	43	0.6	0.5 – 0.9	0.9	0.6 – 1.3	1.1	0.6 – 1.9
	1	78	0.6	0.4 – 0.7	0.8	0.6 – 1.0	1.3	0.9 – 1.8
	2	105	0.5	0.4 – 0.7	0.6	0.5 – 0.8	0.9	0.6 – 1.2
	3+	405	1	-	1	-	1	-
Self-perceived health	Excellent	61	0.7	0.5 – 1.0	0.8	0.6 – 1.1	0.9	0.7 – 1.3
	Good	215	1	-	1	-	1	-
	Fair	163	1.7	1.3 – 2.1	1.7	1.3 – 2.1	1.2	0.9 – 1.6
	Poor	87	4.2	3.1 – 5.6	5.4	3.9 – 7.6	2.7	1.9 – 4.0
Self-reported depression	Depressed	45	1.1	0.8 – 1.5	1.4	1.0 – 2.0	0.7	0.5 – 1.1
Loneliness	Lonely	143	1.9	1.6 – 2.4	1.5	1.2 – 1.9	1.3	1.0 – 1.7
Friendships	No reported friends	465	2.0	1.6 – 2.5	1.7	1.4 – 2.2	1.1	0.9 – 1.5
Smoking	Never	160	1	-	1	-	1	-
	Past	263	1.3	1.0 – 1.6	1.3	1.1 – 1.7	1.2	1.0 – 1.6
	Current	90	1.6	1.2 – 2.1	2.5	1.8 – 3.3	2.1	1.5 – 3.0
Alcohol intake	5 or more days a week	94	0.5	0.4 – 0.7	0.6	0.5 – 0.8	0.9	0.7 – 1.2
	1 – 4 days a week	104	0.4	0.3 – 0.5	0.6	0.5 – 0.8	0.9	0.7 – 1.3
	1 – 4 times every 2 months	80	0.5	0.4 – 0.7	0.6	0.5 – 0.8	1.0	0.7 – 1.4
	0 – 2 times a year	225	1	-	1	-	1	-

Table 3.3: Factors associated with mortality at two years – best fitting model including CFAS I and CFAS II variables

N = 819 in CFAS I, N = 645 in CFAS II total died		CFAS I			CFAS II		
Factor		**n**	**OR**	**95% CI**	**n**	**OR**	**95% CI**
Sex	Women	433	0.5	0.4 – 0.6	349	0.7	0.5 – 0.8
Age (years)	65 – 69	83	1	-	52	1	-
	70 – 74	110	1.5	1.1 – 2.0	75	1.5	1.0 – 2.3
	75 – 79	195	2.5	1.9 – 3.4	96	1.8	1.2 – 2.8
	80 – 84	221	3.2	2.4 – 4.3	160	3.3	2.2 – 4.9
	85 – 89	136	3.6	2.5 – 5.2	143	4.8	3.1 – 7.5
	90+	74	4.9	3.0 – 8.1	117	9.5	5.8 – 15.5
Place of residence	Community	591	1	-	485	1	-
	Semi-dependent housing	81	0.9	0.7 – 1.2	69	1.0	0.7 – 1.4
	Care settings	146	1.5	1.0 – 2.2	89	1.6	0.8 – 3.1
Education (years)	≤9	576	1	-	293	1	-
	10 – 11	112	1.0	0.8 – 1.3	225	0.8	0.6 – 1.1
	≥12	56	1.0	0.7 – 1.3	94	0.7	0.5 – 1.0
Functional Impairment	None	309	1	-	155	1	-
	Mild/Moderate	130	1.6	1.3 – 2.1	120	1.8	1.3 – 2.4
	Severe	352	2.2	1.7 – 2.8	279	4.5	3.3 – 6.1
Dementia and MMSE Score	0 – 17/Dementia	189	3.0	2.1 – 4.2	172	2.1	1.4 – 3.2
	18 – 21	74	2.0	1.4 – 2.7	52	1.9	1.2 – 2.9
	22 – 25	202	1.6	1.3 – 1.9	115	1.2	0.9 – 1.6
	26 – 30	320	1	-	280	1	-
Self-perceived health	Excellent	80	1.0	0.8 – 1.3	61	0.9	0.7 – 1.3
	Good	260	1	-	215	1	-
	Fair	263	1.8	1.5 – 2.3	163	1.1	0.8 – 1.4
	Poor	110	2.6	1.9 – 3.5	87	2.3	1.6 – 3.3
Smoking	Never	231	1	-	160	1	-
	Past	300	1.1	0.9 – 1.3	263	1.2	1.0 – 1.6
	Current	196	1.4	1.1 – 1.8	90	1.9	1.4 – 2.7

3.3.2 Longitudinal attrition

Factors associated with longitudinal attrition univariately and adjusted for other variables in CFAS II are shown in Table 3.4. Unadjusted, individuals were more likely to move or refuse between baseline and two year follow-up if they were a woman, older, lived in semi-dependent or care settings, more deprived, employed in an unskilled occupation, lower educated, single/divorced or widowed, functionally impaired, have dementia or cognitive impairment, have fair or poor self-perceived health, not report friendships, be a current smoker, and drink less often. After adjusting for age the same associations existed.

In a model that included all variables in Table 3.4, those living in care settings and completed further years in education were more likely to be interviewed after two years. Those with unskilled occupations, severe functional impairment, dementia, cognitive impairment or who currently smoke were more likely to move or refuse interview.

After analysing best fit models in CFAS I and CFAS II, all variables in Table 3.5 were included in an adjusted model for both studies. Adjusted for all variables in the table, in both CFAS I and CFAS II, individuals were more likely to participate in the two-year follow up interview if they lived in care settings or completed further years in education. Those who moved or refused were more likely to have an unskilled occupation, have dementia or cognitive impairment, have fewer health conditions, not report friendships and currently smoke. The direction of the association between living in care settings and attrition changed on addition of functional impairment to the model.

There were a few differences in factors associated with refusal or moving between CFAS I and CFAS II. In addition CFAS I individuals were more likely to move or refuse if they were women, or had poor self-perceived health. Those who were widowed in CFAS I were more likely to participate in the two-year follow up interview. In CFAS II those with severe functional impairment and lower alcohol intake were more likely to move or refuse.

Table 3.4: Attrition due to loss in CFAS II

N = 1829 total lost			Unadjusted		Age adjusted		Multivariable	
Factor		**n**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
Sex	Women	1073	1.3	1.1 – 1.4	1.2	1.1 – 1.4	1.1	1.0 – 1.3
Age (years)	65 – 69	408	1	-	1	-	1	-
	70 – 74	429	1.1	1.0 – 1.3	1.1	1.0 – 1.3	1.1	0.9 – 1.2
	75 – 79	406	1.3	1.1 – 1.5	1.3	1.1 – 1.5	1.1	0.9 – 1.3
	80 – 84	315	1.4	1.2 – 1.7	1.4	1.2 – 1.7	1.1	0.9 – 1.4
	85 – 89	195	1.7	1.4 – 2.1	1.7	1.4 – 2.1	1.1	0.8 – 1.5
	90+	78	2.1	1.6 – 3.0	2.1	1.6 – 3.0	1.1	0.7 – 1.6
Place of Residence	Community	1639	1	-	1	-	1	-
	Semi-dependent Housing	129	1.3	1.0 – 1.6	1.2	0.9 – 1.5	1.0	0.8 – 1.3
	Care settings	63	3.2	2.1 – 4.8	2.7	1.7 – 4.1	0.4	0.2 – 1.0
Deprivation	Least deprived	537	0.9	0.8 – 1.0	0.9	0.8 – 1.0	1.0	0.8 – 1.1
	Middle deprived	604	1	-	1	-	1	-
	Most deprived	690	1.3	1.1 – 1.5	1.3	1.1 – 1.4	1.1	0.9 – 1.3
Social class	Skilled	343	0.7	0.6 – 0.8	0.7	0.6 – 0.8	0.9	0.7 – 1.0
	Semi-skilled	915	1	-	1	-	1	-
	Unskilled	399	1.4	1.2 – 1.6	1.4	1.2 – 1.6	1.2	1.0 – 1.4
Education (years)	≤9	570	1	-	1	-	1	-
	10 – 11	931	0.7	0.6 – 0.8	0.8	0.7 – 0.9	0.9	0.8 – 1.1
	≥12	285	0.5	0.4 – 0.6	0.5	0.4 – 0.6	0.7	0.6 – 0.9
Marital Status	Married	991	1	-	1	-	1	-
	Single/divorced	248	1.2	1.0 – 1.4	1.2	1.0 – 1.4	1.0	0.9 – 1.2
	Widowed	578	1.3	1.1 – 1.4	1.1	0.9 – 1.2	0.9	0.8 – 1.1
Functional Impairment	None	1065	1	-	1	-	1	-
	Mild/Moderate	370	1.3	1.1 – 1.5	1.2	1.1 – 1.4	1.0	0.9 – 1.2
	Severe	257	2.0	1.7 – 2.4	1.9	1.6 – 2.3	1.2	1.0 – 1.5
Dementia	Dementia	190	5.8	4.5 – 7.6	5.3	4.0 – 7.0	2.6	1.7 – 4.2
MMSE score	0 – 17	68	3.4	2.4 – 4.9	3.3	2.3 – 4.8	1.1	0.6 – 2.0
	18 – 21	116	2.7	2.1 – 3.4	2.6	2.0 – 3.4	1.5	1.1 – 2.1
	22 – 25	397	2.0	1.7 – 2.3	1.9	1.7 – 2.2	1.6	1.4 – 1.9
	26 – 30	1128	1	-	1	-	1	-
Number of Comorbidities	0	156	1.0	0.8 – 1.2	1.0	0.8 – 1.2	1.1	0.9 – 1.5
	1	306	0.9	0.8 – 1.1	1.0	0.8 – 1.1	1.2	1.0 – 1.4
	2	384	0.9	0.8 – 1.0	0.9	0.8 – 1.1	1.1	0.9 – 1.2
	3+	956	1	-	1	-	1	-
Self-perceived health	Excellent	307	0.9	0.8 – 1.1	0.9	0.8 – 1.1	1.0	0.8 – 1.2
	Good	834	1	-	1	-	1	-
	Fair	432	1.3	1.1 – 1.5	1.3	1.1 – 1.5	1.1	0.9 – 1.3
	Poor	101	1.4	1.1 – 1.8	1.4	1.1 – 1.8	1.1	0.8 – 1.4
Self-reported depression	Depressed	148	1.2	1.0 – 1.5	1.3	1.0 – 1.5	1.1	0.8 – 1.3
Loneliness	Lonely	297	1.2	1.0 – 1.4	1.1	1.0 – 1.3	0.9	0.8 – 1.1
Friendships	No reported friends	1489	1.4	1.2 – 1.7	1.4	1.2 – 1.6	1.1	1.0 – 1.4
Smoking	Never	629	1	-	1	-	1	-
	Past	754	1.0	0.8 – 1.1	1.0	0.8 – 1.1	1.0	0.9 – 1.2
	Current	280	1.4	1.2 – 1.6	1.5	1.2 – 1.7	1.3	1.1 – 1.6
Alcohol intake	5 or more days a week	308	0.6	0.5 – 0.7	0.6	0.5 – 0.7	0.8	0.7 – 1.0
	1 – 4 days a week	446	0.6	0.5 – 0.7	0.6	0.6 – 0.7	0.8	0.7 – 0.9
	1 – 4 times every 2 months	267	0.7	0.6 – 0.8	0.7	0.6 – 0.8	0.8	0.7 – 1.0
	0 – 2 times a year	636	1	-	1	-	1	-

Table 3.5: Factors associated with loss at two years – best fitting model including CFAS I and CFAS II variables

N = 1660 in CFAS I, N = 1829 in CFAS II total lost		CFAS I			CFAS II		
Factor		**n**	**OR**	**95% CI**	**n**	**OR**	**95% CI**
Sex	Women	1106	1.4	1.2 – 1.6	1073	1.1	1.0 – 1.2
Age (years)	65 – 69	424	1	-	408	1	-
	70 – 74	411	1.1	0.9 – 1.3	429	1.1	0.9 – 1.3
	75 – 79	346	0.8	0.7 – 1.0	406	1.1	0.9 – 1.3
	80 – 84	290	0.9	0.8 – 1.2	315	1.1	0.9 – 1.3
	85 – 89	137	0.8	0.6 – 1.1	195	1.1	0.9 – 1.5
	90+	52	1.0	0.6 – 1.6	78	1.1	0.7 – 1.7
Place of Residence	Community	1448	1	-	1639	1	-
	Semi dependent Housing	157	0.9	0.8 – 1.2	129	1.0	0.8 – 1.3
	Care settings	51	0.5	0.3 – 0.9	63	0.4	0.2 – 0.9
Social class	Skilled	359	1.0	0.8 – 1.1	343	0.8	0.7 – 1.0
	Semi-skilled	806	1	-	915	1	-
	Unskilled	448	1.3	1.1 – 1.5	399	1.2	1.0 – 1.4
Education (years)	≤9	1297	1	-	570	1	-
	10 – 11	203	0.8	0.6 – 0.9	931	0.9	0.8 – 1.1
	≥12	122	0.9	0.7 – 1.2	285	0.7	0.6 – 0.9
Marital status	Married	815	1	-	991	1	-
	Single/divorced	189	0.8	0.7 – 1.0	248	1.1	0.9 – 1.3
	Widowed	632	0.8	0.7 – 0.9	578	0.9	0.8 – 1.0
Functional Impairment	None	1114	1	-	1065	1	-
	Mild/Moderate	253	1.1	0.9 – 1.3	370	1.0	0.9 – 1.2
	Severe	266	0.9	0.7 – 1.1	257	1.2	1.0 – 1.5
Dementia and MMSE Score	0 – 17/Dementia	137	3.8	2.8 – 5.2	199	2.5	1.8 – 3.5
	18 – 21	211	4.7	3.8 – 5.9	84	1.6	1.2 – 2.2
	22 – 25	513	2.5	2.2 – 2.9	380	1.7	1.4 – 1.9
	26 – 30	746	1	-	1123	1	-
Number of Comorbidities	0	213	1.4	1.1 – 1.7	156	1.1	0.9 – 1.5
	1	393	1.3	1.1 – 1.5	306	1.2	1.0 – 1.4
	2	359	1.1	0.9 – 1.3	384	1.1	0.9 – 1.2
	3+	694	1	-	956	1	-
Self-perceived health	Excellent	292	1.1	1.0 – 1.3	307	1.0	0.8 – 1.2
	Good	764	1	-	834	1	-
	Fair	443	1.2	1.0 – 1.3	432	1.1	0.9 – 1.3
	Poor	117	1.3	1.0 – 1.8	101	1.1	0.8 – 1.4
Friendships	No reported friends	1235	1.4	1.2 – 1.6	1489	1.2	1.0 – 1.4
Smoking	Never	576	1	-	629	1	-
	Past	603	1.0	0.9 – 1.2	754	1.0	0.9 – 1.2
	Current	431	1.2	1.0 – 1.4	280	1.4	1.1 – 1.6
Alcohol intake	5 or more days a week	NA			308	0.8	0.7 – 0.9
	1 – 4 days a week				446	0.8	0.7 – 0.9
	1 – 4 times every 2 months				267	0.8	0.7 – 1.0
	0 – 2 times a year				636	1	-
Alcohol Usage	Ever	1403	0.9	0.7 – 1.1	NA		
	Never	205	1	-			

3.4 Discussion

Despite initial lower response rates in CFAS II than in the original CFAS I the longitudinal attrition rates were very similar in both studies, with 73% of eligible and alive individuals being seen again (compared to 76% in CFAS I). Age is still the strongest predictor of mortality, however dementia and cognitive impairment had very similar impacts on drop out due to death and longitudinal drop out. Smoking was also associated with mortality and longitudinal attrition in both studies. Women were less likely to die between waves after adjusting for age. Education and social class were found to impact on longitudinal attrition and additionally education was associated with mortality in CFAS II.

3.4.1 Strengths and limitations

This study was able to investigate longitudinal mortality and attrition using similar methodology at two points in time and considered a vast range of variables. The mortality rate seen in CFAS I was higher than in CFAS II due to improving mortality rates over time, however substantial numbers of the older population are still lost from longitudinal studies due to mortality, which is why mortality was considered separately to attrition due to refusal or moving. However, there were some limitations. CFAS I had a two-stage baseline phase such that dementia was only obtained in a subsample. This meant that for the comparison cognitive impairment and dementia were grouped together. The two-stage design also meant individuals could have been seen up to three times before the wave 2 interview in CFAS I (as there was also an annual follow-up on a subset) but for the purposes of this analysis all non-response was included as occurring at the two year interview to provide comparability with CFAS II. Baseline characteristics were self-reported and hence individuals who were already very frail may be less likely to report the factors. However this bias would be consistent for both studies and informant interviews provided additional information on the baseline characteristics. Alcohol consumption was measured differently between the two studies and therefore a direct comparison could not be made of the association between alcohol intake and attrition or mortality.

3.4.2 Interpretation of results

A systematic review found that age and cognitive impairment were the only factors consistently related to longitudinal drop out rather than drop out due to death [77]. This was still the case unadjusted here but age was not found to be associated with longitudinal dropout in either CFAS I or CFAS II when adjusted for other factors in the best fit model. Cognitive impairment has also not always been associated with attrition [116], however it was still found in the wider age range here. New analyses since the systematic review confirm findings from the systematic review on age and cognition [113, 114, 125-134]. Combining results here and results from other studies since the systematic review there now seems to be considerable evidence to support an association between education [78, 118, 119, 128, 131-134], social class [78, 113, 118, 119, 125, 128, 129, 132] and poor self-perceived health [114, 125, 129, 130] with attrition not due to death. Functional impairment was reported in fewer studies as associated with attrition not due to death [114, 125].

There are difficulties with maintaining contact throughout longitudinal studies, the main problem being when participants move homes. Maintaining contact with GP and care home staff could help to re-contact individuals when they move [116]. In CFAS I the Anglia partnership were contacted who would trace people who had moved GPs and see whether they still remained within the study boundaries. To check this in CFAS II a second contact name and address was kept. Many methods also exist to discourage drop-out more generally amongst participants including reminder letters and telephone calls, newsletters and gifts [135]. In both CFAS I and CFAS II newsletters were sent out after each wave of interviews and anyone who participated in focus groups or sub-studies would receive reports on the findings. Other general retention strategies include reducing participant burden [136], for instance providing travel to and from the interview or carrying out the interview at home (which CFAS I and CFAS II did), reimbursement for travel and other expenses incurred by the study, and providing incentives either financial or non-financial through hosting celebratory parties for participants [116, 137]. The best strategy is unknown, but using a variety of methods appears most effective [135, 137, 138].

Even implementing these methods there is normally still drop-out between waves of a study. It is important to carry out analysis on differences between those who drop-out and those who

remain in the study in case analysis needs to be adjusted either through multiple imputation, weighting or external information to be generalizable [128, 139-142].

In a systematic review of the literature on attrition in 2005 Chatfield found limited literature on longitudinal ageing studies undertaking attrition analysis. Since then a greater number of papers on attrition have been published from ageing longitudinal studies [113-116, 127-131, 133, 134, 142, 143]. Some more recent investigations do undertake sensitivity analyses or some form of imputation for missing data [144-148]. However, many studies still do not investigate and report attrition separately to their longitudinal analyses and combine drop out types (deaths and refusals). This makes cross study comparisons complicated, despite guidelines existing for the reporting of these studies [149].

3.4.3 Conclusions

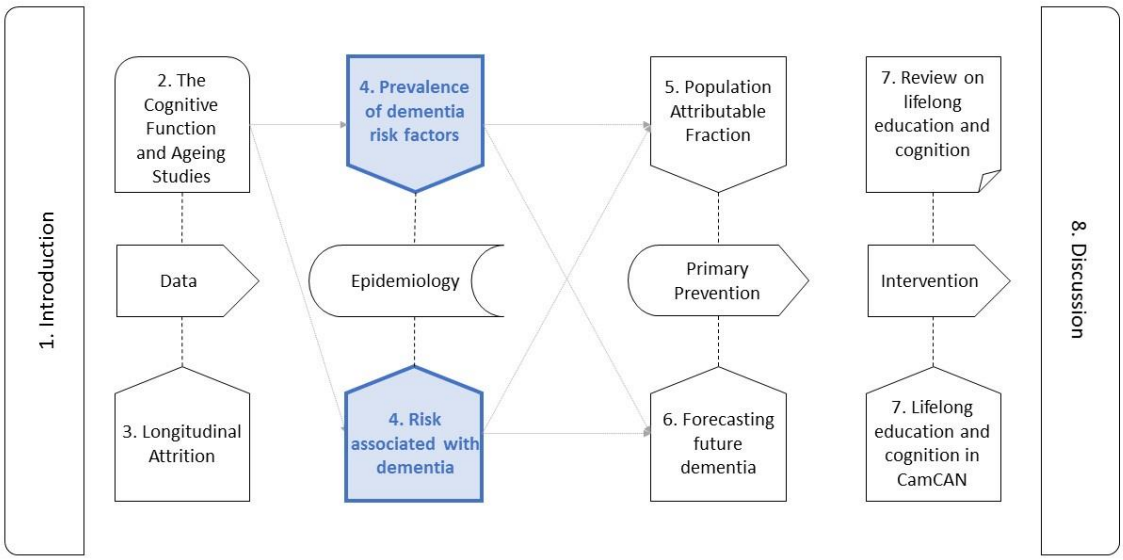
Factors associated with mortality and attrition appear to be fairly stable over time, therefore current methods of analysis that take into account this process and that are now routinely available for widespread usage should provide robust estimates of disease from ongoing longitudinal analysis.

Chapter 4: Risk factor prevalence and Relative Risk comparison

4.1 Chapter overview

Dementia risk has been widely reported, including many reviews and meta-analyses on the subject. Many of these combine relative risk estimates that span many years. Some studies have analysed relative risk of dementia at more than one time point and found temporal changes in risk associated with dementia. However, there is inconsistency about which risk factors temporal changes in dementia associations have occurred in.

The aim of this chapter is to investigate current risk factors for dementia and compare the estimates of relative risk to two decades ago in the UK.



4.2 Background

As previously discussed in Chapter 1 dementia risk has been covered extensively in the literature. There has been less coverage on temporal changes to dementia risk. Given the stability and declining trends seen in dementia prevalence and incidence despite population ageing [9, 10], more literature on the subject is being published. Changes in socio-demographic and cardiovascular risk factors have been shown to contribute to the decline in dementia incidence [21, 150] and dementia prevalence [18, 50] but these studies do not report risk estimates themselves for different generations. Some studies have reported risk estimates for more than one generation. A study from the Netherlands reported different dementia risk estimates between generations for cholesterol and hypertension [49]. Satizabal et al. found decreases in dementia incidence over time in the USA were partially explained by decreases in dementia risk estimates from stroke, heart failure and atrial fibrillation [23].

The prevalence of numerous dementia risk factors are known to be changing over time. Obesity [151, 152], diabetes [153, 154] and stroke [155] prevalence are increasing, whereas prevalence of smoking is decreasing over time [155]. The proportion of people going into higher education is increasing [156, 157] which, given earlier generations' experiences, should impact the proportion of those going on to higher complexity occupations [158]. It follows that if more (or less) of the population are at higher risk of dementia, this will influence prevalence and incidence of dementia itself.

Many dementia risk factors are concurrent and associated with each other. Therefore, adjusting analysis for a broad range of risk factors is essential. Two large randomly sampled population based studies conducted two decades apart were used to analyse changes in prevalence and risk for 37 risk and protective factors of dementia.

4.3 Risk factor prevalence and association with dementia

4.3.1 Methods

The prevalence and relative risk for some risk factors in MRC CFAS have already been primarily published elsewhere [96]. Here, to ensure the appropriate comparisons, the centres from MRC CFAS were restricted to Nottingham, Cambridgeshire and Newcastle (CFAS I) to compare estimates with CFAS II. Both CFAS I and CFAS II have been fully described in Chapter 2.

4.3.1.1 Measures from CFAS I and CFAS II

As described in Chapter 2, study dementia diagnosis using the GMS AGECAT was used to identify prevalent dementia cases at baseline and incident dementia cases at two year follow up.

Both CFAS I and CFAS II include a considerable range of variables that can be investigated as potential risk factors for incident dementia (see [82] and [159] for full details). The questions used to measure risks within this thesis are fully described in Appendix A1. The analysis here includes risk factors from literature and as determined by previous studies. Age and sex in CFAS I and age, sex and place of residence in CFAS II were known for all individuals. Functional disability in ordinary and instrumental activities of daily living (ADL and IADL) was measured using the modified Townsend score [89]. Deprivation was measured by the Townsend deprivation scale [84] split into tertiles. Other risk factors in this analysis were: education (≤9, 10-11, ≥12), marital status (married, single or divorced, widowed), social class (skilled, semi-skilled, unskilled), self-perceived health (excellent, good, fair, poor), smoking (never, quit at least 5 years ago, present smokers and recent ex-smokers), alcohol intake (ever or never consumed an alcoholic drink during lifetime in CFAS I and 5+ days a week, 1-4 days a week, 1-4 times in 2 months, 0-2 times a year in CFAS II), feelings of loneliness, reported friendships and frequency of visits from relatives were all self-reported. Health conditions were also self-reported and included: angina, peripheral vascular disease, heart attack, hypertension, hypotension, transient ischaemic attack, stroke, depression, fits/epilepsy, headaches, head injury, Parkinson's disease, meningitis, arthritis, breathing difficulties, diabetes, peptic ulcers, anaemia, shingles, thyroid, cancer, hearing

difficulties, visual impairment and general anaesthetic. In CFAS I the Rose scale was used for peripheral vascular disease [90].

In CFAS I missing data for risk factors ranged from 0.1% for place of residence and 7.6% for frequency of seeing relatives. Loneliness was measured at the assessment interview so by design missing data had to exceed 80%, and was 82.4%. In CFAS II missing data was between 0.5% for marital status and 14.8% for headaches. Most risk factors in CFAS II had less than 5% missing data. See Chapter 2 for details on missingness for all risk factors.

4.3.1.2 Statistical methods for prevalence

The baseline interview provides the profile of dementia risk factors in the population as the largest proportion of the population is represented before longitudinal attrition occurs, see Chapter 3. Everyone who participated at baseline in CFAS I and CFAS II were included in this analysis including those living in the community, semi-dependent housing or care settings in rural and urban areas.

To ensure population representativeness the prevalence estimates of risk factors at baseline were inverse probability weighted for initial non-response. The weights accounted for the oversampling of those aged 75 years or more, age, sex, deprivation and care home attendance [7].

4.3.1.3 Statistical methods for relative risk comparison

To accurately estimate dementia prevalence and incidence a previous analysis developed a full likelihood model [160, 161] to impute study dementia diagnosis at baseline and at two year follow up for CFAS I and CFAS II. The models have been fully described previously [6]. All individuals from baseline who were alive and participated in the two year follow up interview were modelled. To model dementia prevalence and dementia incidence the model was broken down into four parts:

1. Prevalence of dementia at wave 1 – associated with age and sex.
2. Incidence of dementia at wave 2 – associated with age and sex.
3. Relationship between MMSE, missing MMSE and dementia – associated with age, sex, deprivation, care settings, geographic area and dementia status.
4. Longitudinal attrition – associated with age, sex, deprivation, care status, geographic area, disability, dementia at baseline, MMSE at baseline. Other factors known to be associated with longitudinal attrition [77, 111] were estimated using principal component analysis (CFAS I and CFAS II separately) using the first three components.

Dementia diagnosis was only available for 20% of baseline participants in CFAS I dementia diagnosis was imputed 100 times. Although the same level of imputation was not needed for CFAS II, study dementia diagnosis was imputed the same number of times to be comparable with CFAS I. In addition to dementia diagnosis at baseline and two-year follow up interview being imputed, person-years were also imputed for those who missed the wave two interview (with or without dementia). Those with incident dementia (both known and imputed) were assumed to have developed dementia midway between interviews. All full-likelihood models were estimated using WinBUGS with non-informative uniform priors or flat normal priors for all the parameters and at least 1,000 burn in samples after parameter convergence. Those imputed datasets were used in the risk analysis to match the previously imputed dementia prevalence and incidence.

Chapter 3 showed that those who participated in the two year follow up interview in both CFAS I and CFAS II had certain characteristics compared to those who were lost to follow up due to death, refusal and moving and therefore multiple imputation was used to account for this. The dementia imputations described above, although including risk factors in the models did not impute all the risk factors themselves which therefore had to be imputed separately. It is preferable to impute outcome at the same time as predictors but only the imputed datasets were available at the time this analysis in the thesis was undertaken. A sensitivity analysis was conducted on this (see section 4.6) and there will be more on this in the discussion. Item non-response at baseline for the risk factors was assumed missing at random, where missingness is dependent on information seen within the baseline interview. Risk factor imputed datasets were created using multiple imputation by chained equations. All risk factors named in section 4.3.1.1 were included in the risk factor imputation model: functional impairment, deprivation, education,

marital status, social class, self-perceived health, smoking, alcohol intake, loneliness, reported friendships, frequency of visits from relatives, angina, peripheral vascular disease, heart attack, hypertension, hypotension, transient ischaemic attack, stroke, depression, fits/epilepsy, headaches, head injury, Parkinson's disease, meningitis, arthritis, breathing difficulties, diabetes, peptic ulcers, anaemia, shingles, thyroid, cancer, hearing difficulties, visual impairment and general anaesthetic. If a risk factor was fully reported (such as age and sex) and did not need to be imputed, they were included in the imputation model as covariates as well as the already imputed dementia prevalence and dementia incidence. Risk factors were imputed once in each complete dementia imputed dataset resulting in 100 imputations of dementia and risk factors. Logistic regression was used to impute binary risk factors and multinomial logistic regression if the risk factor was categorical. Years in education were skewed towards compulsory schooling level. Predictive mean matching was therefore a more appropriate method for imputing years in education [162] and ensures all missing data would be within the bounds of observed values. Years in education was then split into three groups after imputation. After risk factors were imputed those with dementia at baseline were excluded.

Risk factor estimates for incident dementia were modelled within each dementia and risk factor imputed dataset using a Poisson regression model adjusted for person-years (as described above). As the imputations did not account for initial non-response all models were inverse probability weighted with the same weights as for the dementia risk factor prevalence, described in section 4.3.1.2. Results were combined over all of the dementia imputations using Rubin's rules [163].

Unadjusted, age and sex adjusted and fully adjusted models were included. The importance of an association was based on the point estimate and estimates of uncertainty such as the 95% confidence interval and p-value [164, 165]. Therefore, as well as using the 95% confidence intervals from the age and sex adjusted models to determine which risk factors should be considered for the fully adjusted model, point estimates of RR≤0.7 or RR≥1.4 when age and sex adjusted were also considered. This was regardless of the 95% confidence intervals as a 30-40% increase or decrease in dementia risk would be substantial at an individual level. The sequential adding of risk factors to the fully adjusted model was done separately in CFAS I and CFAS II. The same rules applied when adding these risk factors sequentially to the fully adjusted model, apart

from Wald tests were also conducted. To provide a temporal comparison the same risk factors needed to be included in the CFAS I and CFAS II fully adjusted models so any risk factors that remained in either of the original fully adjusted models from CFAS I and CFAS II were added to the other. Wald test p-values and 95% confidence intervals are provided for the risk factors that remained in fully adjusted models for both studies. There are several ways to combine results from Wald tests across multiple imputations [166]. The pooling method with the most power was the median P rule [167] but when the outcome was included in imputations, the Type I error for the median P rule was inflated [166]. As it is recommended to include the outcome in the imputations for coefficient estimation [168], two methods of pooling results were used here for comparison – the median P rule and chi pooling. Chi pooling combines the chi-squared values from the Wald tests across the imputations [169] and although the method lacks in power, the Type I error is not inflated when including the outcome in the imputations [166].

4.3.2 Results

There were 7635 participants at baseline in CFAS I, 60.8% were women and average age was 75.6 years (by design). In CFAS II there were 7762 participants at baseline of whom 56.1% were women and average age was 76.4 years (again by design). As reported previously, incidence of dementia per 1,000 person years was 20.0 in CFAS I and 17.7 in CFAS II [6].

4.3.2.1 Prevalence

For point estimate and confidence interval values see Tables 4.1 to 4.3. There was an increase in the proportion of the population who went on to higher education from CFAS I to CFAS II but no change in the level of occupational skill (Table 4.1). More were married and more were living in the community in CFAS II in comparison to CFAS I (Table 4.1). There were large increases in prevalence of self-reported peripheral vascular disease, hypertension and diabetes but transient ischaemic attack declined between the two studies (Table 4.2). Current smoking prevalence declined by 43% of the total whereas never and past smoking prevalence both increased (Table 4.3). Loneliness prevalence remained stable (Table 4.3). Prevalence of stroke and Parkinson's

disease remained constant over time (Table 4.2). Some changes in prevalence were small. Angina prevalence increased slightly between CFAS I and CFAS II (Table 4.2). The prevalence of many neurological diseases remained stable over time but there was a slight decrease in self-reported diagnosed depression from CFAS I to CFAS II and an increase in meningitis prevalence (Table 4.2). There was less severe functional impairment in CFAS II compared to CFAS I but increased prevalence of mild to moderate functional impairment (Table 4.3 – as reported previously [170]).

4.3.2.2 Risk in CFAS I

Relative risk point estimates along with confidence intervals are available in Tables 4.1 to 4.3. Few risk or protective factors were associated with incident dementia after two years when considering their confidence intervals. Those that were associated with higher risk of dementia included older age (Table 4.1), living in care settings (Table 4.1), visual impairment (Table 4.2), poor self-perceived health (Table 4.3) and severe functional impairment (Table 4.3). Several point estimates suggested an association with incident dementia but their confidence intervals extended to include one. Transient ischaemic attack (Table 4.2), stroke (Table 4.2), Parkinson's disease (Table 4.2) and loneliness (Table 4.3) were potentially associated with higher risk of dementia whilst being a woman (Table 4.1), higher education (Table 4.1) and smoking (Table 4.3) were potentially associated with lower risk of dementia. There was no evidence of any association between occupation (Table 4.1), marital status (Table 4.1), deprivation (Table 4.1), hypertension (Table 4.2), diabetes (Table 4.2) or alcohol intake (Table 4.3) and dementia.

Table 4.1: Weighted prevalence and weighted incident rate ratios (IRR) with 95% confidence intervals (CI) of incident dementia for sociodemographic factors at baseline. Full likelihood dementia status and risk factors imputed. Sex adjusted for age and all other risk factors adjusted for age and sex.

		CFAS I					CFAS II				
		n	%	95% CI	IRR	95% CI	n	%	95% CI	IRR	95% CI
Age Group (years)	65-69	1981	25.0	24.0 – 25.9	1	-	1939	23.0	22.1 – 23.9	1	-
	70-74	1776	22.8	21.9 – 23.8	1.2	0.6 – 2.5	1873	22.7	21.8 – 23.7	1.6	0.8 – 3.0
	75-79	1725	22.5	21.6 – 23.4	2.2	1.2 – 4.3	1624	20.5	19.6 – 21.4	3.4	1.8 – 6.3
	80-84	1308	17.7	16.8 – 18.6	4.7	2.5 – 8.6	1278	17.5	16.6 – 18.4	6.9	3.9 – 12.4
	85-89	615	8.5	7.9 – 9.2	6.2	3.3 – 11.7	737	10.5	9.8 – 11.3	8.3	4.4 – 15.7
	≥90	230	3.5	3.1 – 4.0	12.2	5.7 – 26.1	311	5.8	5.2 – 6.6	15.4	7.4 – 32.0
Age group trend (from 65-69 years to ≥90 years)					1.7	1.5 – 1.9				1.7	1.6 – 1.9
Sex	Men	3045	39.2	38.1 – 40.3	1	-	3534	43.9	42.8 – 45.0	1	-
	Women	4590	60.8	59.7 – 61.9	0.7	0.5 – 1.1	4228	56.1	55.0 – 57.2	1.2	0.9 – 1.6
Education	≤9	5529	74.1	73.1 – 75.1	1	-	2047	29.4	28.4 – 30.5	1	-
	10-11	1238	16.6	15.7 – 17.4	0.9	0.5 – 1.4	3923	50.2	49.0 – 51.3	0.7	0.5 – 1.1
	≥12	692	9.3	8.7 – 10.0	0.7	0.4 – 1.3	1667	20.4	19.5 – 21.3	0.7	0.4 – 1.0
Education trend (from ≤9 to ≥12 years)					0.8	0.6 – 1.1				0.8	0.6 – 1.0
Social Class	Skilled	1960	26.5	25.5 – 27.5	0.9	0.6 – 1.3	1958	25.4	24.4 – 26.4	0.9	0.6 – 1.3
	Semi-skilled	3855	52.1	51.0 – 53.3	1	-	3962	54.3	53.2 – 55.5	1	-
	Unskilled	1579	21.4	20.5 – 22.4	1.1	0.7 – 1.6	1370	20.2	19.3 – 21.2	1.5	1.0 – 2.1
Social Class trend (from skilled to unskilled)					1.1	0.9 – 1.4				1.3	1.0 – 1.7
Marital Status	Married	3766	49.6	48.4 – 50.7	1	-	4393	53.7	52.5 – 54.8	1	-
	Single	853	11.4	10.7 – 12.1	1.1	0.7 – 1.9	1005	13.7	12.9 – 14.5	1.4	0.9 – 2.3
	Widowed	2869	39.1	38.0 – 40.2	1.2	0.8 – 1.8	2332	32.7	31.6 – 33.8	1.6	1.1 – 2.3
Marital status trend (from married to widowed)					1.1	0.9 – 1.3				1.3	1.1 – 1.5
Place of residence	Community	6599	86.0	85.2 – 86.8	1	-	7083	89.5	88.7 – 90.3	1	-
	Semi-dependent housing	683	9.1	8.5 – 9.8	1.1	0.7 – 1.8	482	7.2	6.6 – 7.9	1.8	1.1 – 2.7
	Care settings	346	4.8	4.4 – 5.4	2.9	1.7 – 5.2	197	3.3	2.8 – 3.8	5.3	2.4 – 11.5
Place of residence trend (from community to care settings)					1.5	1.2 – 2.0				2.1	1.5 – 2.9
Deprivation tertiles	Least deprived	2467	33.3	32.2 – 34.3	1	-	2576	29.0	28.0 – 30.0	1	-
	Mid-level deprivation	2419	32.8	31.7 – 33.9	1.0	0.7 – 1.5	2620	32.1	31.1 – 33.2	1.3	0.9 – 1.9
	Most deprived	2522	34.0	32.9 – 35.1	1.0	0.6 – 1.5	2566	38.9	37.8 – 40.1	1.3	0.9 – 1.9
Deprivation trend (from least to most deprived)					1.0	0.8 – 1.2				1.1	0.9 – 1.4

4.3.2.3 Risk in CFAS II

When considering their confidence intervals, several risk and protective factors were associated with incident dementia after two years. Older age (Table 4.1), unskilled occupation (Table 4.1), being single or widowed in comparison to married (Table 4.1), living in semi-dependent housing or care settings rather than in the community (Table 4.1), stroke (Table 4.2), Parkinson's disease (Table 4.2), severe functional impairment (Table 4.3) and loneliness (Table 4.3) were associated with higher risk of dementia. Protective associations were indicated for higher education (Table 4.1) and drinking alcohol (Table 4.3). Other point estimates that indicate a potential association with higher risk of dementia include fits/epilepsy (Table 4.2), headaches (Table 4.2), anaemia (Table 4.2), poor self-perceived health (Table 4.3) and smoking (Table 4.3). Meningitis was indicated as a potential protective factor against dementia (Table 4.2). There was no evidence of an association between deprivation (Table 4.1), hypertension (Table 4.2) or diabetes (Table 4.2) and dementia.

4.3.2.4 Risk comparison

Risk of dementia from older age was similar in both studies. Impact of higher education was similar in CFAS I and CFAS II for ≥12 years, but in the later cohort this benefit was also seen for those with 10-11 years education (Table 4.1). Having an unskilled occupation was associated with increased risk of dementia in CFAS II but not in CFAS I (Table 4.1). Other risks such as not being married, and living in non-community settings were stronger in CFAS II than in CFAS I (Table 4.1). Stroke and Parkinson's disease were risk factors in both CFAS I and CFAS II (Table 4.2). Visual impairment was associated with increased risk of dementia in CFAS I but not CFAS II (Table 4.2). Higher risk of dementia for those who had poor self-perceived health in comparison with good self-perceived health was found in both studies, with a slight reduction in strength of association in CFAS II (Table 4.3). Functional impairment and loneliness maintained a similar risk association across both studies (Table 4.3). Whereas in CFAS I there was no association between smoking, past or present, and risk of dementia, in CFAS II there was a higher risk of dementia for current smokers (Table 4.3). There was increased risk of dementia for individuals who barely drink alcohol in CFAS II, which had not been seen in CFAS I (Table 4.3). In CFAS I the trend for self-perceived

health from good to poor was important whereas in CFAS II it was not. Otherwise all trends were the same between the two studies, an important trend was shown for alcohol in CFAS II with reduced risk with increasing reported intake, but this could not be tested in CFAS I. Age, place of residence, Parkinson's disease and functional impairment were important risk factors in the fully adjusted model in both CFAS I and CFAS II. In addition sex, visual impairment and smoking were important in the CFAS I fully adjusted model but not CFAS II and alcohol intake was important in the CFAS II fully adjusted model (Table 4.4). The p-values from chi pooling and the median P rule gave similar results for individual categories of risk factors. When looking at risk factors for the variable as a whole there are differences between the two methods, for instance if based on only the chi pooling p-value age group, place of residence and functional impairment overall do not contribute to the fully adjusted model whereas based on the median P rule p-values the variables overall do contribute to the fully adjusted model.

Table 4.2: Presence of health conditions at baseline with weighted prevalence and weighted incidence rate ratio (IRR) with 95% confidence intervals (CI) of incident dementia. Full likelihood dementia status and risk factors imputed. All risk factors adjusted for age and sex.

		CFAS I					CFAS II				
		n	%	95% CI	IRR	95% CI	n	%	95% CI	IRR	95% CI
Vascular Disease	Angina	1011	13.4	12.6 – 14.1	1.0	0.7 – 1.6	1168	16.0	15.2 – 16.9	1.2	0.8 – 1.7
	Peripheral Vascular Disease	320	4.3	3.8 – 4.7	1.2	0.6 – 2.5	784	10.7	10.0 – 11.4	1.2	0.8 – 1.8
	Heart attack	761	10.2	9.5 – 10.9	1.1	0.7 – 1.9	832	11.5	10.8 – 12.3	1.0	0.7 – 1.6
	Hypertension	2346	30.9	29.9 – 32.0	0.9	0.6 – 1.3	3943	52.3	51.2 – 53.5	0.9	0.7 – 1.2
	Transient ischaemic attack	1203	15.9	15.1 – 16.8	1.4	0.9 – 2.1	681	9.0	8.4 – 9.7	1.2	0.8 – 2.0
	Stroke	601	8.0	7.4 – 8.6	1.5	0.9 – 2.4	636	8.9	8.2 – 9.6	1.5	1.0 – 2.2
Neurological Disease	Self-reported depression	884	11.8	11.1 – 12.5	1.1	0.6 – 1.8	579	7.9	7.3 – 8.5	1.0	0.5 – 1.9
	Fits/epilepsy	156	2.1	1.8 – 2.4	1.2	0.4 – 3.8	164	2.2	1.9 – 2.6	1.7	0.7 – 3.9
	Headaches	813	10.9	10.3 – 11.7	1.1	0.7 – 1.8	676	10.4	9.7 – 11.2	1.4	0.9 – 2.3
	Head injury	901	12.0	11.3 – 12.8	1.1	0.7 – 1.8	837	11.3	10.6 – 12.1	1.2	0.8 – 1.9
	Parkinson's disease	78	1.1	0.8 – 1.3	2.3	0.8 – 6.5	71	0.9	0.7 – 1.2	2.9	1.1 – 8.1
	Meningitis*	64	0.8	0.7 – 1.1	-	-	154	2.0	1.7 – 2.4	0.6	0.2 – 2.4
Other medical history	Arthritis	3988	53.5	52.3 – 54.6	1.1	0.8 – 1.5	4091	55.0	53.8 – 56.1	1.1	0.8 – 1.5
	Breathing difficulties	1455	19.2	18.3 – 20.1	1.1	0.7 – 1.6	1465	19.7	18.8 – 20.7	1.0	0.7 – 1.5
	Diabetes	471	6.2	5.7 – 6.8	1.0	0.5 – 2.0	1079	14.5	13.6 – 15.3	0.9	0.6 – 1.5
	Peptic Ulcers	765	10.2	9.5 – 10.9	0.9	0.5 – 1.6	625	8.5	7.8 – 9.1	1.2	0.7 – 2.0
	Anaemia	210	2.8	2.5 – 3.2	0.9	0.4 – 2.4	210	3.0	2.6 – 3.4	1.5	0.7 – 3.1
	Shingles	1761	23.8	22.8 – 24.8	0.9	0.6 – 1.3	1761	23.5	22.6 – 24.5	0.8	0.6 – 1.2
	Thyroid	438	5.8	5.3 – 6.4	1.3	0.7 – 2.2	696	9.7	9.0 – 10.4	1.1	0.7 – 1.7
	Hearing Difficulties	1682	22.5	21.6 – 23.5	1.1	0.8 – 1.6	1981	26.9	25.8 – 27.9	0.9	0.7 – 1.3
	Visual impairment	1007	13.6	12.9 – 14.4	1.7	1.1 – 2.4	1083	15.2	14.4 – 16.1	1.1	0.8 – 1.7
	General Anaesthetic	3430	46.0	44.9 – 47.1	0.8	0.6 – 1.1	6055	80.1	79.2 – 81.1	0.9	0.6 – 1.3

* Meningitis results not shown for CFAS I, confidence interval inflated due to low numbers

Table 4.3: Weighted prevalence and weighted incidence rate ratio (IRR) with 95% confidence intervals (CI) for other potential risk factors and incident dementia. Full likelihood dementia status and risk factors imputed. All risk factors adjusted for age and sex.

		CFAS I					CFAS II				
		n	%	95% CI	IRR	95% CI	n	%	95% CI	IRR	95% CI
Self-perceived Health	Excellent	1313	17.7	16.8 – 18.6	0.8	0.5 – 1.4	1484	19.4	18.5 – 20.3	0.9	0.6 – 1.4
	Good	3666	49.4	48.3 – 50.6	1	-	3812	50.7	49.5 – 51.8	1	-
	Fair	1944	26.3	25.3 – 27.3	1.2	0.8 – 1.8	1712	23.9	22.9 – 24.9	1.3	0.9 – 1.9
	Poor	494	6.7	6.1 – 7.2	2.0	1.2 – 3.4	427	6.1	5.5 – 6.7	1.6	0.9 – 3.0
Self-perceived health trend (from excellent to poor)					1.3	1.1 – 1.6				1.2	1.0 – 1.5
Functional Impairment	None	5236	68.5	67.4 – 69.6	1	-	4978	63.4	62.3 – 64.6	1	-
	Mild/moderate	1048	14.1	13.3 – 14.9	1.3	0.8 – 2.0	1498	21.1	20.1 – 22.1	1.1	0.8 – 1.7
	Severe	1267	17.5	16.6 – 18.3	2.4	1.6 – 3.6	1002	15.5	14.6 – 16.5	2.5	1.7 – 3.7
Functional impairment trend (from none to severe)					1.6	1.3 – 1.9				1.6	1.3 – 1.9
Loneliness	Not lonely	1043	78.8	75.4 – 81.9	1	-	6220	82.3	81.4 – 83.2	1	-
	Lonely	303	21.2	18.1 – 24.6	1.4	0.8 – 2.4	1248	17.7	16.8 – 18.6	1.4	1.0 – 1.9
Friendships	Does not report friendships	1423	19.2	18.3 – 20.1	1.3	0.9 – 1.9	1126	15.3	14.5 – 16.2	1.0	0.7 – 1.6
	Reports friendships	6043	80.9	79.9 – 81.7	1	-	6541	84.7	83.8 – 85.5	1	-
Meets relatives frequently	Less than weekly	1580	22.4	21.4 – 23.4	0.9	0.6 – 1.3	1657	22.4	21.4 – 23.4	1.0	0.7 – 1.4
	At least weekly	5475	77.6	76.6 – 78.6	1	-	5578	77.6	76.6 – 78.6	1	-
Smoking	Never	2547	34.8	33.7 – 35.9	1	-	2909	38.3	37.2 – 39.5	1	-
	Past	3001	40.3	39.1 – 41.4	0.7	0.5 – 1.1	3598	47.6	46.4 – 48.7	1.1	0.8 – 1.5
	Current	1879	24.9	24.0 – 25.9	0.8	0.5 – 1.3	1037	14.1	13.3 – 15.0	1.5	0.9 – 2.3
Smoking trend (from never to current)					0.9	0.7 – 1.1				1.2	0.9 – 1.5
Alcohol intake	Ever	6639	89.3	88.6 – 90.0	1	-	NA				
	Never	782	10.7	10.0 – 11.4	1.0	0.6 – 1.7	NA				
	5 or more days a week	NA					1553	20.4	19.5 – 21.4	0.5	0.3 – 0.8
	1-4 days a week	NA					2215	29.4	28.3 – 30.4	0.5	0.3 – 0.7
	1-4 times in 2 months	NA					1243	16.6	15.8 – 17.5	0.6	0.4 – 0.9
	0-2 times a year	NA					2353	33.6	32.5 – 34.7	1	-
Alcohol intake trend (from 5+ days a week to 0-2 times a year)										1.3	1.1 – 1.5

Table 4.4: Estimates for incidence rate ratio (IRR) associated with incident dementia after two years with 95% confidence intervals (CI), adjusted for all variables in table. P-values from Wald tests combined over imputations by using the chi-squared (C-p) or by using the median (M-p). P-values for whole variable in the reference category line.

		CFAS I				CFAS II			
		IRR	95% CI	C-p	M-p	IRR	95% CI	C-p	M-p
DEMOGRAPHICS									
Age Group (years)	65-69	1	-	0.38	0.00	1	-	0.20	0.00
	70-74	1.2	0.6 – 2.5	0.45	0.37	1.4	0.7 – 2.7	0.32	0.27
	75-79	2.1	1.1 – 4.1	0.03	0.01	2.7	1.4 – 5.1	0.00	0.00
	80-84	3.7	1.9 – 7.4	0.00	0.00	4.9	2.6 – 9.2	0.00	0.00
	85-89	4.3	2.0 – 9.1	0.00	0.00	4.7	2.3 – 9.8	0.00	0.00
	≥90	6.4	2.5 – 16.7	0.00	0.00	8.1	3.5 – 18.8	0.00	0.00
Sex	Men	1	-			1	-		
	Women	0.6	0.4 – 0.9	0.02	0.00	0.9	0.6 – 1.3	0.51	0.48
Education	≤9	1	-	0.80	0.39	1	-	0.84	0.56
	10-11	0.9	0.5 – 1.5	0.53	0.52	0.9	0.6 – 1.3	0.46	0.43
	≥12	0.8	0.4 – 1.5	0.41	0.31	0.9	0.5 – 1.5	0.58	0.56
Social class	Skilled	0.9	0.6 – 1.4	0.59	0.58	1.0	0.6 – 1.5	0.66	0.66
	Semi-skilled	1	-	0.89	0.67	1	-	0.62	0.25
	Unskilled	1.0	0.6 – 1.5	0.58	0.56	1.3	0.9 – 1.9	0.18	0.13
Marital status	Married	1	-	0.85	0.60	1	-	0.62	0.25
	Single	1.0	0.6 – 1.8	0.60	0.62	1.1	0.7 – 1.8	0.67	0.67
	Widowed	1.0	0.7 – 1.6	0.52	0.47	1.3	0.9 – 2.0	0.17	0.11
Place of residence	Community	1	-	0.20	0.01	1	-	0.13	0.01
	Semi-dependent housing	1.0	0.6 – 1.7	0.66	0.73	1.5	1.0 – 2.4	0.07	0.04
	Care settings	2.2	1.2 – 3.9	0.01	0.00	3.3	1.3 – 7.9	0.01	0.01
HEALTH CONDITIONS									
Transient Ischaemic Attack		1.2	0.8 – 1.8	0.40	0.31	1.0	0.6 – 1.7	0.75	0.76
Stroke		1.0	0.6 – 1.8	0.64	0.65	1.1	0.7 – 1.8	0.63	0.67
Fits/epilepsy		1.1	0.3 – 3.3	0.61	0.60	1.1	0.4 – 2.8	0.71	0.73
Headaches		0.9	0.6 – 1.5	0.55	0.56	1.2	0.8 – 2.0	0.37	0.29
Parkinson's Disease		1.6	0.6 – 4.8	0.36	0.29	1.8	0.6 – 5.6	0.31	0.30
Anaemia		0.9	0.3 – 2.3	0.61	0.65	1.1	0.5 – 2.4	0.71	0.74
Visual impairment		1.4	0.9 – 2.1	0.11	0.06	0.9	0.6 – 1.4	0.70	0.68
OTHER									
Self-perceived health	Excellent	0.9	0.6 – 1.6	0.59	0.55	1.0	0.6 – 1.5	0.67	0.68
	Good	1	-	0.93	0.44	1	-	0.98	0.86
	Fair	1.0	0.6 – 1.5	0.64	0.66	1.0	0.7 – 1.4	0.69	0.73
	Poor	1.3	0.7 – 2.4	0.39	0.32	1.0	0.5 – 2.0	0.69	0.74
Functional impairment	None	1	-	0.27	0.02	1	-	0.21	0.01
	Mild/moderate	1.1	0.7 – 1.9	0.52	0.48	1.0	0.6 – 1.5	0.67	0.70
	Severe	1.7	1.1 – 2.8	0.03	0.01	1.7	1.1 – 2.6	0.03	0.01
Loneliness	Not lonely	1	-			1	-		
	Lonely	1.3	0.7 – 2.4	0.32	0.10	1.1	0.7 – 1.6	0.63	0.61
Smoking	Never	1	-	0.50	0.09	1	-	0.86	0.63
	Past	0.7	0.5 – 1.1	0.12	0.05	1.1	0.8 – 1.5	0.61	0.59
	Current	0.7	0.5 – 1.2	0.21	0.14	1.2	0.7 – 1.9	0.49	0.46
Alcohol intake	Ever	1	-			NA			
	Never	1.0	0.6 – 1.7	0.59	0.59	NA			
	5 or more days a week	NA				0.6	0.4 – 1.0	0.03	0.02
	1-4 days a week	NA				0.6	0.4 – 0.9	0.02	0.01
	1-4 times in 2 months	NA				0.6	0.4 – 1.0	0.05	0.03
	0-2 times a year	NA				1	-	0.40	0.01

4.4 CFAS II risk factors only relative risk analysis

4.4.1 Methods

Some variables were available in CFAS II that were not available in CFAS I and were therefore not included in the risk comparison analysis. These risk factors included hypotension, cancer and physical inactivity. All were self-reported and binary. Physical inactivity was defined from three questions – someone was physically inactive if they did not take part in any mild, moderate or vigorous physical activity. As the level of item non-response in CFAS II does not require 100 imputations a separate analysis on all risk factors in CFAS II was completed with 20 imputations of dementia and risk factors together. Dementia, risk factors and date difference between baseline and the second wave of interviews were imputed with the same methods as in section 4.3.1.3.

4.4.2 Results

Number of people with hypotension, cancer or physically inactive and weighted prevalence are shown in Table 4.5. Including these risk factors in the imputations could impact the imputations for other risk factors so results for all risk factors are shown in Tables 4.6 to 4.8. Mostly, the same risk factors were highlighted as important as in the risk comparison analysis but in addition, deprivation (Table 4.6), hypotension (Table 4.7), head injury (Table 4.7), shingles (Table 4.7) and physical inactivity (Table 4.8) were also shown to be important and anaemia was no longer important in this analysis (Table 4.7).

Table 4.5: Number of people with hypotension, cancer and who are physically inactive at baseline in CFAS II with prevalence (%) and 95% confidence intervals (CI).

Risk factor	n	%	95% CI
Hypotension	520	7.0	6.4 – 7.6
Cancer	1103	14.6	13.8 – 15.4
Physically inactive	480	7.5	6.8 – 8.1

Table 4.6: Demographic factors at baseline and risk of incident dementia. Estimates for incidence rate ratio (IRR) with 95% confidence intervals (CI). Dementia and risk factors imputed together 20 times for all CFAS II risk factors. Sex adjusted for age and all other risk factors adjusted for age and sex.

		CFAS II	
		IRR	95% CI
Age Group (years)	65-69	1	-
	70-74	1.7	0.9 – 3.3
	75-79	3.7	2.1 – 6.7
	80-84	7.5	4.2 – 13.5
	85-89	9.8	5.4 – 17.6
	≥90	16.9	8.7 – 32.8
Age group trend (from 65-69 years to ≥90 years)		1.8	1.6 – 1.9
Sex	Men	1	-
	Women	1.3	1.0 – 1.7
Education	≤9	1	-
	10-11	0.7	0.5 – 1.0
	≥12	0.5	0.3 – 0.8
Education trend (from ≤9 to ≥12 years)		0.7	0.6 – 0.9
Social Class	Skilled	0.8	0.5 – 1.1
	Semi-skilled	1	-
	Unskilled	1.6	1.1 – 2.3
Social Class trend (from skilled to unskilled)		1.5	1.2 – 1.9
Marital Status	Married	1	-
	Single	1.5	0.9 – 2.6
	Widowed	1.9	1.4 – 2.6
Marital status trend (from married to widowed)		1.4	1.2 – 1.6
Place of residence	Community	1	-
	Semi-dependent housing	1.9	1.2 – 2.9
	Care settings	6.6	3.2 – 13.6
Place of residence trend (from community to care settings)		2.3	1.6 – 3.1
Deprivation tertiles	Least deprived	1	-
	Mid-level deprivation	1.4	1.0 – 2.1
	Most deprived	1.5	1.1 – 2.2
Deprivation trend		1.2	1.0 – 1.4

Table 4.7: Presence of health conditions at baseline and risk of incident dementia. Estimates for incidence rate ratio (IRR) with 95% confidence intervals (CI). Dementia and risk factors imputed together 20 times for all CFAS II risk factors. All health conditions adjusted for age and sex.

		CFAS II	
		IRR	95% CI
Vascular Disease	Angina	1.3	0.8 – 1.9
	Peripheral Vascular Disease	1.2	0.8 – 1.9
	Heart attack	1.1	0.7 – 1.7
	Hypertension	0.8	0.6 – 1.1
	Hypotension	1.6	0.9 – 2.6
	Transient ischaemic attack	1.2	0.7 – 2.0
	Stroke	1.7	1.1 – 2.6
Neurological Disease	Self-reported depression	1.1	0.6 – 2.0
	Fits/epilepsy	2.1	1.0 – 4.6
	Headaches	1.4	0.9 – 2.1
	Head injury	1.5	0.9 – 2.3
	Parkinson's disease	4.3	1.4 – 13.1
	Meningitis	0.7	0.2 – 2.9
Other medical history	Arthritis	1.1	0.8 – 1.5
	Breathing difficulties	1.1	0.7 – 1.6
	Diabetes	1.0	0.6 – 1.5
	Peptic Ulcers	1.3	0.8 – 2.1
	Anaemia	1.3	0.6 – 2.7
	Shingles	0.7	0.5 – 1.0
	Thyroid	1.1	0.7 – 1.8
	Cancer	1.2	0.8 – 1.8
	Hearing Difficulties	0.9	0.7 – 1.3
	Visual impairment	1.2	0.8 – 1.8
	General Anaesthetic	0.8	0.6 – 1.2

Table 4.8: Other potential risk factors and incident dementia. Estimates for incidence rate ratio (IRR) with 95% confidence intervals (CI). Dementia and risk factors imputed together 20 times for all CFAS II risk factors. All other risk factors adjusted for age and sex.

		CFAS II	
		IRR	95% CI
Self-perceived Health	Excellent	1.0	0.6 – 1.6
	Good	1	-
	Fair	1.5	1.1 – 2.2
	Poor	2.1	1.2 – 3.8
Self-perceived health trend (from excellent to poor)		1.3	1.1 – 1.6
Functional Impairment	None	1	-
	Mild/moderate	1.3	0.9 – 2.0
	Severe	3.6	2.5 – 5.3
Functional impairment trend (from none to severe)		1.9	1.6 – 2.3
Loneliness	Not lonely	1	-
	Lonely	1.6	1.2 – 2.2
Friendships	Does not report friendships	1.3	0.8 – 2.0
	Reports friendships	1	-
Meets relatives frequently	Less than weekly	1.0	0.7 – 1.4
	At least weekly	1	-
Smoking	Never	1	-
	Past	1.1	0.8 – 1.6
	Current	1.7	1.1 – 2.7
Smoking trend (from never to current)		1.3	1.0 – 1.6
Alcohol intake	5 or more days a week	0.3	0.2 – 0.6
	1-4 days a week	0.4	0.3 – 0.6
	1-4 times in 2 months	0.5	0.3 – 0.8
	0-2 times a year	1	-
Alcohol intake trend (from 5+ days a week to 0-2 times a year)		1.5	1.3 – 1.8
Physical activity	Active	1	-
	Inactive	3.0	2.0 – 4.4

4.5 Complete case analysis

Multiple imputation reporting guidelines recommend presenting results from complete case analysis for comparison with multiple imputation analysis [171]. Reasons for any differences should then be discussed.

4.5.1 Methods

For complete case analysis in CFAS I the sample was restricted to participants who took part in the A0 assessment interview and the C2 combined screening and assessment interview. See section 2.2.2 for flow through interviews. Everyone who participated in the screening interview S0 who did not go through to assessment had to be excluded as their study dementia diagnosis was unknown. Analysis on those who participated in C2 need to be inverse probability weighted to ensure population representativeness. Variables from S0 were used for C2 weights and included age, sex, MMSE group and number of health conditions. Weights for C2 were then multiplied by the same S0 weights described in section 4.3.1.2 for initial non-response.

4.5.2 Results

After excluding individuals who did not participate in the C2 interview and those who had dementia at the A0 interview, 746 participants were included in the CFAS I complete case analysis. In CFAS II after excluding those who did not take part in wave two interviews and those who had dementia at baseline interview, 5183 participants were included in the CFAS II complete case analysis. Results for complete cases analysis in CFAS I and CFAS II are given in Tables 4.9 to 4.11. Results were stable between the 100 imputed datasets and complete case analysis for CFAS II. Comparing the two CFAS I analyses, results were similar between the 100 imputed datasets analysis and the complete case analysis. Some risk factors had a stronger association with dementia in the complete case analysis than the imputed analysis, for instance, education and poor self-perceived health. Other factors were not associated with dementia in the imputed analysis but were associated with dementia in the complete case analysis, for instance semi-dependent housing, headaches, breathing difficulties, peptic ulcers and anaemia.

Table 4.9: Complete case analysis estimates of incident dementia risk from demographic risk factors at baseline. Sex adjusted for age, all other risk factors adjusted for age and sex. All inverse probability weighted.

		CFAS I		CFAS II	
		IRR	95% CI	IRR	95% CI
Age Group (years)	65-69	1	-	1	-
	70-74	1.4	0.5 – 3.8	1.7	0.8 – 3.3
	75-79	1.9	0.8 – 4.8	3.6	1.9 – 6.7
	80-84	3.4	1.4 – 8.2	7.4	4.1 – 13.3
	85-89	4.9	1.9 – 12.6	8.8	4.7 – 16.6
	≥90	16.7	5.6 – 49.8	13.9	6.6 – 28.9
Sex	Men	1	-	1	-
	Women	1.1	0.6 – 2.0	1.2	0.9 – 1.7
Education	≤9	1	-	1	-
	10-11	1.0	0.5 – 1.9	0.6	0.4 – 1.0
	≥12	0.3	0.1 – 0.9	0.5	0.3 – 0.9
Social Class	Skilled	0.8	0.5 – 1.5	0.9	0.6 – 1.3
	Semi-skilled	1	-	1	-
	Unskilled	0.8	0.4 – 1.8	1.6	1.1 – 2.4
Marital Status	Married	1	-	1	-
	Single	0.9	0.3 – 2.1	1.7	1.0 – 2.9
	Widowed	0.9	0.4 – 1.6	1.8	1.3 – 2.7
Place of residence	Community	1	-	1	-
	Semi-dependent housing	2.0	1.0 – 4.1	2.1	1.3 – 3.4
	Care settings	3.9	1.5 – 10.1	8.3	3.8 – 17.8
Deprivation tertiles	Least deprived	1	-	1	-
	Mid-level deprivation	1.0	0.5 – 1.9	1.4	1.0 – 2.1
	Most deprived	0.9	0.5 – 1.6	1.3	0.9 – 2.0

Table 4.10: Complete case analysis estimates of incident dementia risk from health condition risk factors at baseline. All adjusted for age and sex and inverse probability weighted.

		CFAS I		CFAS II	
		IRR	95% CI	IRR	95% CI
Vascular Disease	Angina	0.8	0.4 – 1.6	1.3	0.9 – 2.0
	Peripheral Vascular Disease	1.2	0.3 – 5.6	1.3	0.8 – 2.1
	Heart attack	1.2	0.6 – 2.3	1.1	0.6 – 1.8
	Hypertension	0.9	0.5 – 1.6	0.9	0.7 – 1.2
	Transient ischaemic attack	1.5	0.8 – 2.6	1.4	0.8 – 2.3
	Stroke	1.3	0.6 – 2.8	1.7	1.1 – 2.7
Neurological Disease	Self-reported depression	1.0	0.4 – 2.3	1.0	0.5 – 1.8
	Fits/epilepsy	1.4	0.3 – 7.2	1.5	0.7 – 3.6
	Headaches	0.5	0.2 – 1.3	1.5	0.9 – 2.6
	Head injury	0.7	0.3 – 1.5	1.2	0.7 – 1.8
	Parkinson's disease	2.2	0.4 – 11.9	3.6	1.3 – 10.3
	Meningitis*	-	-	0.5	0.1 – 2.2
Other medical history	Arthritis	1.3	0.7 – 2.2	1.2	0.8 – 1.6
	Breathing difficulties	1.7	1.0 – 3.0	1.0	0.7 – 1.5
	Diabetes	0.8	0.2 – 3.0	0.9	0.5 – 1.4
	Peptic Ulcers	2.0	0.8 – 4.7	1.3	0.8 – 2.2
	Anaemia	2.6	0.7 – 9.2	1.6	0.8 – 3.4
	Shingles	1.0	0.6 – 1.9	0.7	0.5 – 1.1
	Thyroid	1.1	0.5 – 2.6	1.1	0.7 – 1.8
	Hearing Difficulties	1.3	0.8 – 2.2	1.0	0.7 – 1.4
	Visual impairment	2.0	1.1 – 3.4	1.1	0.8 – 1.7
	General Anaesthetic	0.8	0.5 – 1.4	0.8	0.6 – 1.2

* Meningitis results not shown for CFAS I as confidence interval was inflated due to low numbers

Table 4.11: Complete case analysis estimates of incident dementia risk from other risk factors. All adjusted for age and sex and inverse probability weighted.

		CFAS I		CFAS II	
		IRR	95% CI	IRR	95% CI
Self-perceived Health	Excellent	0.9	0.4 – 2.2	0.9	0.6 – 1.5
	Good	1	-	1	-
	Fair	1.8	1.0 – 3.3	1.5	1.0 – 2.1
	Poor	5.5	2.7 – 11.1	2.1	1.1 – 4.1
Functional Impairment	None	1	-	1	-
	Mild/moderate	1.4	0.6 – 2.9	1.1	0.7 – 1.8
	Severe	3.2	1.7 – 6.0	3.6	2.4 – 5.4
Loneliness	Not lonely	1	-	1	-
	Lonely	1.2	0.7 – 2.1	1.5	1.0 – 2.1
Friendships	Does not report friendships	1.7	1.0 – 3.2	1.2	0.8 – 1.9
	Reports friendships	1	-	1	-
Meets relatives frequently	Less than weekly	0.5	0.2 – 1.2	1.0	0.6 – 1.4
	At least weekly	1	-	1	-
Smoking	Never	1	-	1	-
	Past	0.5	0.3 – 0.9	1.1	0.7 – 1.6
	Current	0.6	0.3 – 1.3	1.6	1.0 – 2.6
Alcohol intake	Ever	1	-	NA	
	Never	1.4	0.6 – 3.0		
	5 or more days a week	NA		0.4	0.2 – 0.6
	1-4 days a week			0.4	0.2 – 0.6
	1-4 times in 2 months			0.5	0.3 – 0.8
	0-2 times a year			1	-

4.6 Sensitivity analysis

4.6.1 Methods

Sensitivity analysis was conducted in CFAS II to compare estimates when imputing risk factors within the dementia imputed datasets with imputing dementia and risk factors at the same time. For computation reasons it was not possible to impute dementia and all risk factors together 100 times as this results in a dataset too large for the statistical package. To complete the sensitivity analysis 20 of the dementia imputed datasets with risk factors imputed after dementia were compared to 20 imputed datasets where dementia and risk factors were imputed at the same time. Binary risk factors and dementia were imputed using logistic regression and multinomial

logistic regression was used if the risk factor was categorical. Education was imputed using predictive mean matching and then coded into three groups after being imputed. Date difference between baseline and the second wave of interviews was imputed using predictive mean matching and then coded into person years, as described in section 4.3.1.3.

4.6.2 Results

Tables 4.12 to 4.14 give the results from the sensitivity analysis comparing imputations where risk factors are imputed after dementia to imputations where dementia and risk factors are imputed at the same time. Some associations are slightly attenuated in the analysis where risk factors are imputed after dementia, for instance education, stroke and smoking but within the bounds of the original estimates. Widths of the confidence intervals remained similar. Results based on only 20 of the imputed datasets where dementia was imputed before risk factors align closely to results from the full 100 datasets.

Table 4.12: Demographic factors at baseline and risk of incident dementia. Comparing estimates from 20 imputations where risk factors were imputed within dementia imputed datasets to dementia and risk factors being imputed at the same time. Estimates for incidence rate ratio (IRR) with 95% confidence intervals (CI). Sex adjusted for age and all other risk factors adjusted for age and sex.

		CFAS II			
		Risk factors imputed after dementia		**Dementia and risk factors imputed together**	
		IRR	95% CI	IRR	95% CI
Age Group (years)	65-69	1	-	1	-
	70-74	1.6	0.8 – 3.0	1.8	0.9 – 3.6
	75-79	3.4	1.8 – 6.3	3.6	1.9 – 6.9
	80-84	6.9	3.8 – 12.5	7.5	4.0 – 13.9
	85-89	8.0	4.2 – 15.4	10.0	5.3 – 18.9
	≥90	15.5	7.7 – 31.1	17.6	8.9 – 35.1
Age group trend (from 65-69 years to ≥90 years)		1.7	1.6 – 1.9	1.8	1.6 – 2.0
Sex	Men	1	-	1	-
	Women	1.2	0.9 – 1.6	1.2	0.9 – 1.6
Education	≤9	1	-	1	-
	10-11	0.7	0.5 – 1.1	0.7	0.5 – 0.9
	≥12	0.7	0.4 – 1.1	0.5	0.3 – 0.8
Education trend (from ≤9 to ≥12 years)		0.8	0.6 – 1.0	0.7	0.6 – 0.9
Social Class	Skilled	0.9	0.6 – 1.3	0.8	0.5 – 1.2
	Semi-skilled	1	-	1	-
	Unskilled	1.5	1.0 – 2.1	1.6	1.1 – 2.3
Social Class trend (from skilled to unskilled)		1.3	1.0 – 1.7	1.4	1.2 – 1.8
Marital Status	Married	1	-	1	-
	Single	1.4	0.9 – 2.2	1.6	0.9 – 2.9
	Widowed	1.6	1.1 – 2.4	1.9	1.3 – 2.6
Marital status trend (from married to widowed)		1.3	1.0 – 1.6	1.4	1.1 – 1.6
Place of residence	Community	1	-	1	-
	Semi-dependent housing	1.7	1.1 – 2.7	1.9	1.3 – 3.0
	Care settings	5.3	2.5 – 11.4	7.1	3.4 – 14.5
Place of residence trend (from community to care settings)		2.0	1.5 – 2.8	2.3	1.7 – 3.2
Deprivation tertiles	Least deprived	1	-	1	-
	Mid-level deprivation	1.3	0.9 – 1.9	1.4	1.0 – 2.1
	Most deprived	1.3	0.9 – 1.9	1.5	1.0 – 2.1
Deprivation trend (from least to most deprived)		1.1	0.9 – 1.3	1.2	1.0 – 1.4

Table 4.13: Presence of health conditions at baseline and risk of incident dementia. Comparing estimates from 20 imputations where risk factors were imputed within dementia imputed datasets to dementia and risk factors being imputed at the same time. Estimates for incidence rate ratio (IRR) with 95% confidence intervals (CI). Dementia and risk factors imputed together 20 times for CFAS I risk factors only. All health conditions adjusted for age and sex.

		CFAS II			
		Risk factors imputed after dementia		**Dementia and risk factors imputed together**	
		IRR	95% CI	IRR	95% CI
Vascular Disease	Angina	1.2	0.9 – 1.8	1.2	0.9 – 1.8
	Peripheral Vascular Disease	1.2	0.8 – 1.9	1.3	0.8 – 2.0
	Heart attack	1.1	0.7 – 1.7	1.1	0.7 – 1.7
	Hypertension	0.9	0.7 – 1.2	0.8	0.6 – 1.1
	Transient ischaemic attack	1.2	0.8 – 1.9	1.3	0.8 – 2.0
	Stroke	1.5	1.0 – 2.3	1.7	1.1 – 2.6
Neurological Disease	Self-reported depression	1.0	0.5 – 1.8	1.0	0.5 – 1.9
	Fits/epilepsy	1.7	0.7 – 3.9	2.0	0.8 – 4.9
	Headaches	1.4	0.9 – 2.3	1.4	0.8 – 2.4
	Head injury	1.2	0.8 – 1.9	1.4	0.9 – 2.1
	Parkinson's disease	2.8	1.0 – 7.8	4.8	1.9 – 12.0
	Meningitis	0.7	0.2 – 2.8	0.5	0.1 – 2.4
Other medical history	Arthritis	1.1	0.8 – 1.4	1.1	0.8 – 1.5
	Breathing difficulties	1.1	0.7 – 1.6	1.0	0.7 – 1.5
	Diabetes	0.9	0.6 – 1.4	0.9	0.6 – 1.4
	Peptic Ulcers	1.3	0.7 – 2.1	1.4	0.8 – 2.4
	Anaemia	1.6	0.8 – 3.3	1.5	0.8 – 2.9
	Shingles	0.8	0.6 – 1.2	0.7	0.5 – 1.0
	Thyroid	1.1	0.7 – 1.7	1.1	0.7 – 1.8
	Hearing Difficulties	0.9	0.7 – 1.3	0.9	0.7 – 1.3
	Visual impairment	1.1	0.8 – 1.7	1.3	0.8 – 1.9
	General Anaesthetic	0.9	0.6 – 1.3	0.9	0.6 – 1.3

Table 4.14: Other potential risk factors and incident dementia. Comparing estimates from 20 imputations where risk factors were imputed within dementia imputed datasets to dementia and risk factors being imputed at the same time. Estimates for incidence rate ratio (IRR) with 95% confidence intervals (CI). Dementia and risk factors imputed together 20 times for CFAS I risk factors only. All other risk factors adjusted for age and sex.

		CFAS II			
		Risk factors imputed after dementia		Dementia and risk factors imputed together	
		IRR	95% CI	IRR	95% CI
Self-perceived Health	Excellent	0.9	0.6 – 1.4	0.9	0.6 – 1.5
	Good	1	-	1	-
	Fair	1.3	0.9 – 1.9	1.5	1.1 – 2.0
	Poor	1.6	0.9 – 2.9	2.1	1.1 – 3.8
Self-perceived health trend (from excellent to poor)		1.2	1.0 – 1.5	1.3	1.1 – 1.6
Functional Impairment	None	1	-	1	-
	Mild/moderate	1.2	0.8 – 1.8	1.2	0.8 – 1.9
	Severe	2.6	1.7 – 3.8	3.6	2.4 – 5.5
Functional impairment trend (from none to severe)		1.6	1.3 – 2.0	1.9	1.5 – 2.4
Loneliness	Not lonely	1	-	1	-
	Lonely	1.3	1.0 – 1.9	1.6	1.1 – 2.2
Friendships	Does not report friendships	1.1	0.7 – 1.6	1.3	0.9 – 1.8
	Reports friendships	1	-	1	-
Meets relatives frequently	Less than weekly	1.0	0.7 – 1.4	1.0	0.7 – 1.5
	At least weekly	1	-	1	-
Smoking	Never	1	-	1	-
	Past	1.1	0.8 – 1.6	1.1	0.8 – 1.6
	Current	1.6	1.0 – 2.5	1.8	1.1 – 2.8
Smoking trend (from never to current)		1.2	1.0 – 1.5	1.3	1.0 – 1.6
Alcohol intake	5 or more days a week	0.5	0.3 – 0.8	0.4	0.2 – 0.6
	1-4 days a week	0.5	0.3 – 0.8	0.4	0.2 – 0.6
	1-4 times in 2 months	0.5	0.3 – 0.9	0.5	0.3 – 0.7
	0-2 times a year	1	-	1	-
Alcohol intake trend (from 5+ days a week to 0-2 times a year)		1.3	1.1 – 1.6	1.5	1.3 – 1.8

4.7 Further exploratory analysis

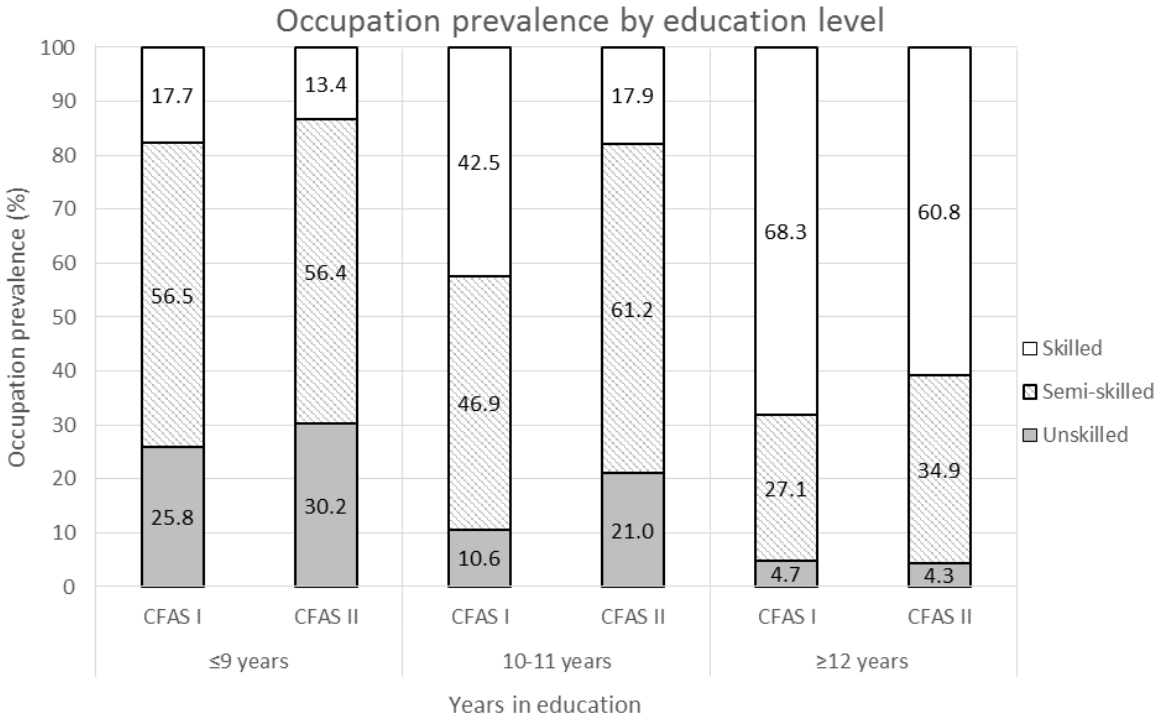
4.7.1 Methods

Results that merited further exploration of data within the study were analysed in greater depth. Occupation level by education level was explored for CFAS I and CFAS II. Prevalence of number of health conditions by level of alcohol consumption was explored in CFAS II only as there was a difference in how alcohol consumption was measured between CFAS I and CFAS II. Risk of dementia from physical inactivity stratified by functional impairment group was estimated in CFAS II only as physical inactivity was not measured in CFAS I

4.7.2 Results

The proportion of those going into further education has increased over time. Although an increase in the level of highly skilled occupations over time would be expected, overall occupation level has remained stable over time. Estimates of occupation level by education level revealed that this was not the case for all education levels. Whilst occupation level for those with ≤9 years of education and ≥12 years of education remained relatively stable over time, occupation level for those with 10-11 years of education changed over time. A lower proportion of those with 10-11 years of education continued to highly skilled occupations in CFAS II compared to CFAS I (Figure 4.1). There was an increase in the proportion of those with 10-11 years of education going into semi-skilled and even unskilled occupations between CFAS I and CFAS II (Figure 4.1).

Figure 4.1: Occupation level by education level in CFAS I and CFAS II.



There was a protective association seen between alcohol intake and dementia in CFAS II that was not present in CFAS I. Often doctors recommend abstaining from alcohol if someone becomes ill. Further analysis in CFAS II showed that whilst most people have three or more health conditions, those who drink infrequently had the largest proportion with three or more health conditions, 66% of those who drink 0-2 times a year (Table 4.15).

Table 4.15: Number of people in each health condition and alcohol intake group and weighted percentage of people with either 0, 1, 2 or 3+ health conditions by alcohol intake.

	Number of health conditions excluding dementia				
Alcohol intake	0	1	2	3+	Total %
5 or more days a week	122 (7.6%)	279 (17.3%)	346 (21.7%)	806 (53.5%)	100
1-4 days a week	174 (7.5%)	398 (17.5%)	528 (23.4%)	1115 (51.6%)	100
1-4 times in 2 months	61 (4.6%)	187 (14.5%)	254 (19.9%)	741 (61.0%)	100
0-2 times a year	110 (4.4%)	271 (10.8%)	434 (18.4%)	1538 (66.4%)	100

In CFAS II physical inactivity was associated with a large increase in risk of dementia. However, this association could be because physical inactivity was acting as a proxy for functional impairment. There was a low prevalence of physical inactivity in both the no functional impairment and mild/moderate functional impairment groups (Table 4.16) reflected in the wide confidence intervals when estimating risk (Table 4.17). However, the stratified analysis still shows an increase in risk of dementia in the no functional impairment and mild/moderate functional impairment groups (Table 4.17).

Table 4.16: Percentage of people who are active and inactive by functional disability in CFAS II.

	Physical inactivity		
Functional impairment	Active	Inactive	Total %
None	4953 (99.6%)	22 (0.5%)	100
Mild/moderate	1412 (94.4%)	83 (5.7%)	100
Severe	550 (59.4%)	355 (40.6%)	100

Table 4.17: Relative risk of dementia from physical inactivity in each functional impairment group, unadjusted and adjusted for age and sex

	Functional impairment	RR	95% CI
Unadjusted	None	2.5	0.3 – 19.0
	Mild/moderate	1.9	0.7 – 4.9
	Severe	1.6	1.0 – 2.7
Age and sex adjusted	None	2.4	0.3 – 19.4
	Mild/moderate	1.8	0.7 – 4.7
	Severe	1.5	0.9 – 2.5

4.8 Discussion

For a summary of prevalence results see Figure 4.2 and for a summary of risk results see Figure 4.3. This analysis shows that the protective association of ≥12 years of education with dementia was similar between the two studies but in addition 10-11 years of education was a protective factor in CFAS II. Having an unskilled occupation was not associated with dementia in CFAS I but was associated with increased risk of dementia in CFAS II. Whilst more people are staying in

education longer now than before, this has not led to a greater proportion being in higher skilled occupations. Widowhood was not associated with dementia in CFAS I but was associated with dementia in CFAS II though less people were widowed in CFAS II compared to CFAS I. Living in semi-dependent housing was not associated with dementia in CFAS I but was associated with increased risk of dementia in CFAS II even though slightly less people lived in semi-dependent housing in CFAS II compared to CFAS I. Current smoking was not associated with dementia in CFAS I but was associated with increased risk of dementia in CFAS II at the same time as smoking prevalence having decreased over time. Visual impairment was associated with increased risk of dementia in CFAS I but was not associated with dementia in CFAS II, and the prevalence of visual impairment has remained stable over time. Although alcohol consumption could not be directly compared between the two studies there was no indication of abstinence from drinking being associated with dementia in CFAS I whereas drinking more than 0-2 times a year was associated with decreased risk of dementia in CFAS II. Living in care settings, stroke, Parkinson's disease, poor self-perceived health, severe functional impairment and loneliness were associated with increased risk of dementia in both studies. There were slight decreases in the proportion of individuals living in care settings and prevalence of severe functional impairment and loneliness but prevalence remained similar for stroke, Parkinson's disease and poor self-perceived health. Although transient ischaemic attack, diabetes, hypertension, peripheral vascular disease and general anaesthetic were not associated with dementia, their prevalence changed over time. There was a decrease in prevalence of transient ischaemic attack whereas diabetes, hypertension, peripheral vascular disease and general anaesthetic increased in prevalence over time.

Figure 4.2: Summary of prevalence results

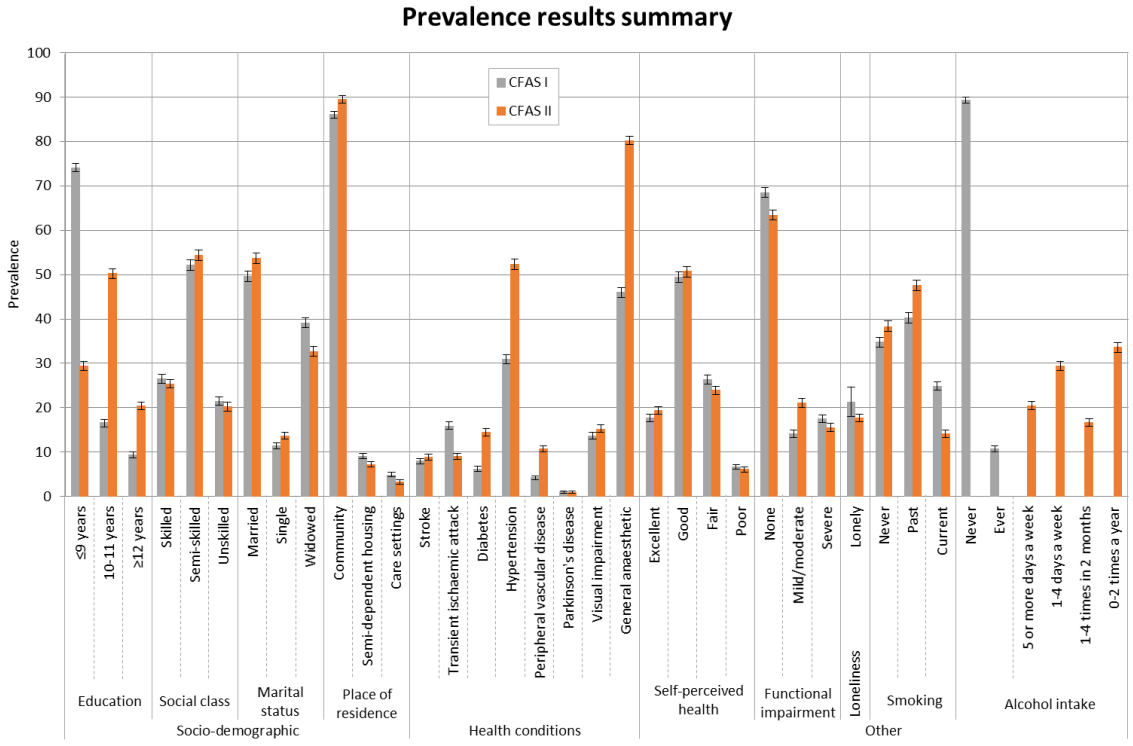
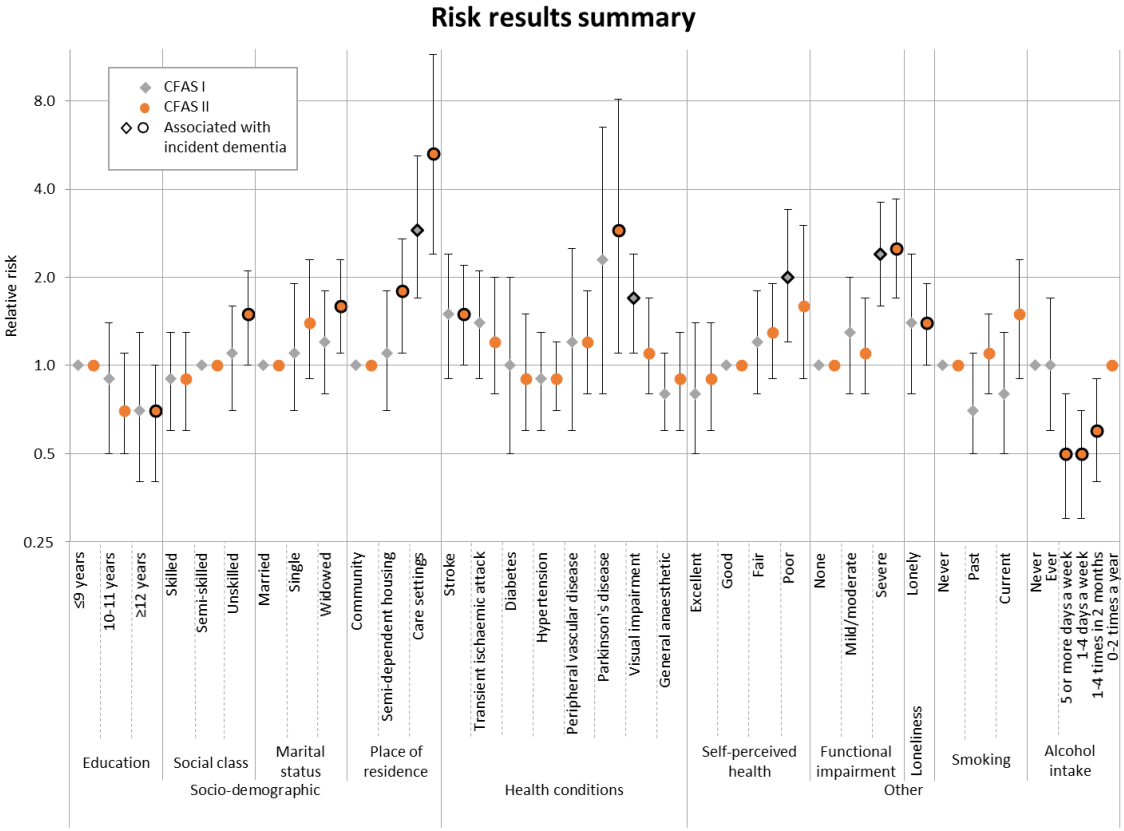


Figure 4.3: Summary of important relative risk results for CFAS I and CFAS II



4.8.1 Strengths and limitations

The main strength of this study was the population sampling technique. People aged 65 years and over were randomly sampled in the same three locations in the UK, chosen to span rural and city areas and individuals living in the community, semi-dependent housing and care settings. Both studies were large enough that risk factors could be compared across time and could be fully adjusted. The clinical diagnosis of dementia has been changing over time whereas the algorithmic approach used in CFAS I and CFAS II was identical and therefore a direct comparison could be made. Informant interviews for those with cognitive and physical impairment could be used for information on the risk factors. As with all analyses there were limitations. Although there was a change in baseline response rate between CFAS I and CFAS II (fully discussed in Chapter 2), inverse probability weights were used to ensure population representativeness. All those who died between baseline and two-year follow-up interview were excluded from analysis. Those with cognitive impairment/dementia and with some of the risk factors (such as education, functional impairment and smoking) were more likely to die between waves (Chapter 3) and therefore these risk estimates could be conservative. Dementia incidence was measured after two years making direction of association between risk factors and dementia difficult to determine as individuals could already be in early stage cognitive impairment when risk factor status was established. This would especially be the case for risk factors such as living in care settings and functional impairment. However, shorter follow up means that risk factor status is less likely to change between the two interviews compared to longer follow up periods. The fully adjusted models in CFAS I and CFAS II had to contain the same risk factors to give a temporal comparison. The risk factors important to the CFAS I fully adjusted model and CFAS II fully adjusted model were not necessarily the same and inclusion of those important to both may have attenuated some results. CFAS I and CFAS II randomly sampled those aged 65 years or over so could not determine midlife risk factors for dementia. Alcohol intake was measured differently in CFAS I and CFAS II – in CFAS I participants were asked whether or not they had ever drunk alcohol (binary) whereas CFAS II asked how often a participant had drunk alcohol in a certain period of time (categorical).

4.8.1.1 Strengths and limitations to multiple imputation

As suggested by multiple imputation reporting guidelines [171], complete case analysis for dementia risk was completed. CFAS II estimates from the complete case analysis were all within bounds of the multiple imputation analysis on 100 imputed datasets. In CFAS I the association was generally stronger for the risk factors in the complete case analysis compared to the imputed analysis. Excluding the outcome from the imputation could falsely weaken an association [171] and this could have occurred here as dementia was imputed prior to the risk factors. The changes in estimates from CFAS I could result in different conclusions for temporal changes in dementia risk. An example of this is dementia risk from loneliness. Currently loneliness increases risk of dementia in both studies but in the complete case analysis loneliness only increases risk of dementia in CFAS II. Given there are no changes in conclusions from the CFAS II complete case analysis, only for the CFAS I analysis, it is more likely that changes in CFAS I estimates are from the level of missingness in the outcome dementia. In CFAS II the complete case analysis was still based on 5183 participants whereas in CFAS I, due to study design, the complete case analysis was restricted to 746 participants. This is reflected by wide confidence intervals for the CFAS I complete case analysis. Given the low prevalence of some of the risk factors originally at baseline, the numbers end up being small for some analysis, for instance out of the 746 included in the analysis only 7 had peptic ulcers at baseline and went on to develop dementia. Therefore the estimates from the 100 imputed datasets are considered more reliable than the complete case analysis. Risk factor missingness was assumed missing at random for imputation analysis. Given the wide range of risk factors included in the imputation model, this assumption is likely to hold.

CFAS I was a two-stage design at baseline so dementia assessment was completed on a subsample. To account for this 100 full likelihood dementia imputations were undertaken. Risk factor item non-response was imputed once within each of the 100 dementia imputations in both studies, resulting in 100 imputed datasets of dementia and risk factors. Previous research has shown that it is preferable to impute the outcome at the same time as predictor variables [168]. Although the outcome (dementia) was included in the model when imputing the risk factors, dementia had already been imputed beforehand using a different model. Not including predictors and outcome in the same imputation model could result in falsely weakened associations. As it

was necessary to use datasets where dementia had already been imputed to match previous analysis, sensitivity analysis was conducted in CFAS II. The sensitivity analysis for CFAS II compared 20 imputed datasets where dementia was imputed before the risk factors to 20 imputed datasets where dementia was imputed with risk factors. The same sensitivity analysis would not be informative in CFAS I as study dementia diagnosis was only conducted on 20% of participants and therefore imputing only 20 times would give inaccurate results. However, results from CFAS I here were similar to previously published results for MRC CFAS [96]. There is little literature on secondary imputation, however, research has shown that multiple imputation is robust to extent of missingness and sample size when the outcome is included in the model [172]. The sensitivity analysis showed little difference in results when comparing imputations that imputed dementia before the risk factors to imputing dementia with the risk factors. Results from the sensitivity analysis were all within bounds of the original analysis but results where dementia and risk factors were imputed together were generally stronger. In most cases this would not change the conclusions of temporal changes in dementia risk, however for deprivation instead of there being no association with dementia in either CFAS I or CFAS II, there was an association only in CFAS II in the sensitivity analysis suggesting that deprivation may now be associated with dementia. In future analyses imputing dementia and risk factors together would be recommended to ensure the strength of associations are not attenuated. This would potentially change dementia prevalence and incidence estimates published for CFAS I and CFAS II.

4.8.2 Interpretation of results

CFAS I baseline began in 1991 and CFAS II in 2008 with follow-up interviews after two years. A study from the USA analysed five-year incident dementia risk at four time points 1977-1983, 1986-1991, 1992-1998 and 2004-2008 [23], the timing of CFAS I and CFAS II correspond best with the final two samples respectively. De Bruijn et al. compared incident dementia risk with a mean follow up of 8 years in 1990 and 2000 in the Netherlands [49], the timing of CFAS I corresponds best with the first sample. Similar to between CFAS I and CFAS II, the American study showed that risk of dementia from smoking had increased between 1992 and 2008 [23] but the study from the Netherlands found risk of dementia from smoking had decreased between 1990 and 2000 [49]. The American study found that risk of dementia from prevalent and interim stroke decreased vastly between 1977 and 2008 [23]. Risk of dementia from only prevalent stroke (comparable to stroke measurement in CFAS I and CFAS II used here) increased from 1992 to 2008 [23] whereas

dementia risk from stroke remained stable between CFAS I and CFAS II. The association between low education and increased risk of dementia became stronger over time in the Dutch study [49]. In the American study the protective association of higher education strengthened initially from 1977 to 1991 but similarly to between CFAS I and CFAS II stabilised from 1992 to 2008 [23]. There are mixed results on the trends in dementia risk from stroke and smoking but agreement that the protective association between higher education and dementia has remained stable over time. Comparisons between these studies may not be feasible due to differences between countries, the points in time for which analysis was conducted and length of follow-up.

Despite early inconsistency there is now sustained and consistent evidence between current smoking and higher risk of dementia [173-179]. Early case-control studies could be biased as diagnostic criteria for Alzheimer's disease specified that a person could not already have cardiovascular conditions, more likely excluding participants who smoked earlier in life [180]. The change in evidence between CFAS I and CFAS II could be explained by reduced life expectancy from smoking in CFAS I. In the last two decades, the life expectancy of smokers has increased and are therefore reaching ages at increased risk of developing dementia. Between the two studies a public space smoking ban across the UK came into effect and evidence suggests this ban has reduced exposure to second hand smoke [181]. This could be contributing to change in risk as second hand smoke is risk factor for dementia [182-184] and therefore non-smokers (the referent) would be at lower risk now than before.

Stroke increased risk of dementia in both CFAS I and CFAS II supporting previous findings [185-187]. People who have had a stroke are now living longer than before and are reaching ages where dementia is of increased risk [188-190]. Although stroke prevalence has remained stable here, stroke incidence has reduced in recent years [191], even though milder forms of stroke are now being detected that would previously have been labelled as transient ischaemic attack. Trends in dementia risk from stroke over time may differ between countries depending on whether increasing survival outweighs milder stroke being detected.

Low education was identified as a risk factor for dementia early on [192, 193] but it was suggested that these results could be due to methodological and ascertainment biases [194].

There is now substantial evidence for higher education as a protective factor for dementia [195-197], both prevalent [198-203] and incident [204-206]. Another study concluded that the strengthening association between education and dementia may be because World War II disrupted education for many of the participants in the older cohort, but not the younger one [49]. For CFAS I and CFAS II, World War I and World War II respectively would have disrupted education for many participants. Between CFAS I and CFAS II the 1944 Education Act was implemented [207]. This abolished secondary school fees and increased compulsory school leaving age making further schooling accessible to many more children and accounting for the increase in prevalence of 10-11 years of education. Grammar schools were also introduced providing high quality schooling based on attainment to those who could not afford private schools which would in turn open opportunities to higher education in university. This could explain the slightly stronger protective association of higher education seen in CFAS II compared to CFAS I.

Having an unskilled occupation increased risk of dementia in CFAS II but not in CFAS I, consistent with findings from other studies [195, 208-210]. The change in risk could be explained by World War I and World War II disrupting working life as many participants in CFAS I would have lived through two world wars whereas most participants in CFAS II would have experienced World War II but not World War I. Further analysis of CFAS I and CFAS II showed that although overall occupation levels remained stable over time, this was not true within each education group. There could be many reasons for this, one could be that employers look for above average education – in CFAS I the majority had ≤9 years education whereas in CFAS II the majority had 10-11 years of education. Other reasons could include that more professions may now require higher qualifications, such as nursing and teaching or that previously it was possible to enter a workplace at a lower level requiring fewer qualifications and work up to more highly skilled occupations.

Between CFAS I and CFAS II dementia risk from increasing age was similar but in CFAS II more people were in the older age groups. Population ageing has occurred in Western countries due to improved health care, increased life expectancy and increased birth rate after World War II. Increased life expectancy has probably led to less people being widowed. Being single or widowed was associated with increased risk of dementia and could be a measure for social isolation. This is supported by findings on loneliness in CFAS I and CFAS II, with the association

remaining stable over time. Loneliness and social isolation have previously been reported as associated with increased risk of dementia [211-214].

Visual impairment was a strong risk factor for dementia in CFAS I but no longer increased risk in CFAS II. Prevalence of visual impairment was similar between the two studies. Diabetes can result in complications such as diabetic retinopathy [215], with visual impairment caused by increased severity. Although diabetes prevalence is increasing over time, the use of the medication metformin has also increased [153] which is associated with decreased risk of diabetic retinopathy in comparison to other medications [216]. This could be contributing to the trend in dementia risk from visual impairment. A National Health Service (NHS) paper from 2000 suggested that cataract surgery should be made more accessible on the NHS [217]. Cataracts has a large impact on visual impairment and if more cataract surgeries were made available between CFAS I and CFAS II this could also be contributing to the decreasing trend in dementia risk from visual impairment.

Alcohol intake was measured differently in CFAS I and CFAS II so was not directly comparable. There was no association between abstinence from alcohol consumption and dementia in CFAS I. In CFAS II higher alcohol consumption was associated with decreased risk of dementia. There is conflicting evidence on alcohol consumption and dementia. Some have found that drinking moderately could reduce risk of dementia [36, 218, 219]. Others have found that high alcohol consumption in the form of alcohol use disorders increases risk of dementia [220]. Recently, it has been shown that the association could be dependent on the numbers of units consumed rather than the frequency (as measured in CFAS II), with abstainers and those who drink >14 units per week at higher risk of dementia [221]. If people who drink frequently, for instance in CFAS II drink 5 or more days a week, still drink less than 14 units per week, this could explain the decreased risk from drinking seen in CFAS II where alcohol abstinence is the referent. This analysis also did not take into account the type of alcohol consumed. Other studies have shown that increased risk of dementia from alcohol abstinence was attributable to the greater risk of cardiometabolic disease in that group [221]. Doctors often recommend alcohol abstinence when these health conditions are diagnosed. Further analysis in CFAS II showed that the proportion with 3 or more health conditions was higher in those who infrequently drink compared to those who frequently

drink supporting the concept that the protective association has at least an element of health confounding.

The prevalence of hypertension and diabetes increased over time but neither were associated with risk of dementia. Recent research suggests that cardiovascular health conditions are risk factors for dementia in midlife rather than in later life [36, 46]. The shorter follow up in this analysis could account for the reason why no association was seen. Another reason could be that good treatment management has led to no increase in risk. For a while, use of anti-hypertensive medication was suggested as a prevention for dementia but a systematic review combining evidence found no protective effect of anti-hypertensive drugs [222].

Some risk factors were only included in CFAS II. As discussed in Chapter 1 evidence on physical inactivity as a risk factor is mixed [223, 224]. Later life physical inactivity is likely to be associated with increased risk of dementia as those with dementia are likely to have functional impairment. Further analysis in CFAS II showed that even in those with no functional impairment there was increased risk of dementia. However numbers were small and therefore the results were inconclusive.

4.8.3 Conclusions

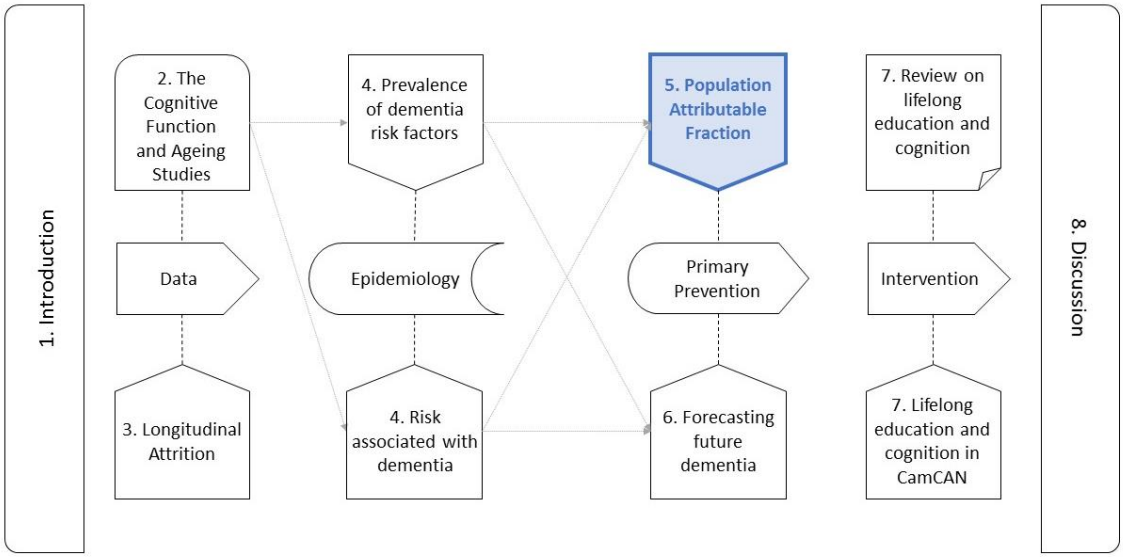
In conclusion, many risk factors for dementia have changed over time, either in prevalence, risk association or both. Changes in risk association with dementia could be due to many reasons: the level at which the risk factor is detected; advances in medication and care; or improved lifestyle factors, but this needs further research. Knowing how risk factors interact with dementia and how this has changed over time can help inform prevention strategies in the future. Some risk factors, such as stroke, Parkinson's disease and loneliness were consistently associated with increased risk of dementia and therefore remain robust targets for intervention. High educational and occupational attainment have become more prominent protective factors for dementia so encouraging engagement in educational and occupational activities could protect against dementia. The changing prevalence and risk associated with dementia risk factors means that their impact on dementia will also change. This will be investigated in the following chapter.

Chapter 5: Population Attributable Fraction

5.1 Chapter overview

The previous chapter showed that the prevalence of dementia risk factors and relative risk associated with dementia from some, not all, of those risk factors is changing over time. The Population Attributable Fraction (PAF) of dementia estimates the percentage of dementia cases associated with each risk factor based on the prevalence of dementia risk factors and their relative risk. Given that both are changing over time, the PAFs of dementia are also likely to change over time. The current chapter examines PAFs associated with dementia at two time points using CFAS I and CFAS II.

PAF of dementia at death has been studied in MRC CFAS before with a focus on neuropathological measures of dementia [225]. Apart from age there is no overlap between the risk factors considered previously and this work.



5.2 Background on PAF in dementia research

Dementia prevention is becoming more important in many countries as the older population increases. Dementia is a complex syndrome with many likely causal factors and given there are currently no curative interventions the best option for the future is to address factors known to contribute to risk. Risk factors for dementia have been widely researched and many are modifiable [36]. Interventions for modifiable risk factors could help prevent dementia. Recently there has been an abundance of research on the Population Attributable Fraction (PAF) of modifiable risk factors for dementia, estimating that combined PAF for dementia is between 8.4% and 54.1% [37, 38, 47, 49, 173, 226-233]. This estimate narrows to between 28.2% and 48.4% for studies that consider more than four risk factors and fully adjust the combined PAF estimate [38, 47, 49, 232, 233].

Results from other countries may not provide representative estimates for the UK as risk factor profiles are likely to differ. Norton et al. show that the percentage of dementia cases associated with risk factors differs between countries, for instance lower education is associated with 7.3% of dementia cases in the USA whereas in the UK low education is associated with 12.2% of incident dementia cases [38]. Previously for the UK combined PAF for dementia has been estimated as 30.0% when adjusted for other risk factors, this does not include some confounders, such as age and sex [38].

In the Netherlands, estimates of combined dementia PAF increased over time when including body mass index, hypertension, diabetes, cholesterol, smoking and education [49]. This was also true for a separate combined dementia PAF model that included stroke, coronary heart disease, heart failure and atrial failure [49]. Individual dementia PAF for hypertension increased over time [49]. However, comparisons across time were not always possible as to calculate PAF relative risk has to be above one and with the same reference categories at both time points this was not always the case. There is more on this in the next section.

Chapter 4 showed that prevalence of dementia risk factors and risk associated with dementia have changed over time in the UK. Therefore PAF for dementia will also be changing and there are no comparisons of PAF over time for the UK. Accurate estimates of PAF are essential when planning prevention strategies. The main aim here is to provide current dementia PAF estimates for the UK to help inform prevention strategies. Other aims include comparing the PAF now to two decades ago given changes in risk factors over time and producing a combined PAF for the percentage of incident dementia cases associated with all risk factors considered here.

5.3 Background on Attributable Fractions and Attributable Risks

The terms Population Attributable Fraction (PAF) and Population Attributable Risk (PAR) have been used interchangeably. They are however two separate measures. The PAF has also been known as the PAR% and the aetiologic fraction [234, 235].

Attributable risk is defined as the number of prevalent or incident disease cases attributable to an exposure. The attributable fraction is defined as the proportion or percentage of prevalent or incident disease cases attributable to an exposure. Gordis described four separate measures [236], the attributable risk and attributable fraction can be applied to either the exposure group or the entire population. Here, the attributable risk and the attributable fraction for the exposure group will be named the Exposed Attributable Risk (EAR) and the Exposed Attributable Fraction (EAF) respectively. The EAR and EAF are important because some people with the disease in the exposed group would have developed the disease whether or not they had been exposed. Therefore the EAR and EAF can measure the number or proportion respectively of prevalent or incident disease cases from the exposure group that would be associated with the exposure. The EAR and EAF are calculated using:

$$EAR = Disease\ rate\ in\ exposed\ group - Disease\ rate\ in\ unexposed\ group$$

and

$$EAF = \frac{Disease\ rate\ in\ exposed\ group - Disease\ rate\ in\ unexposed\ group}{Disease\ rate\ in\ exposed\ group}.$$

Public health interventions operate at national levels and this is where the Population Attributable Risk (PAR) and Population Attributable Fraction (PAF) are helpful. This is because the population is made of exposed and unexposed people and those in the unexposed group will normally have a different prevalence or incidence of disease to the exposed group. If the prevalence of an exposure is low this could limit the efficacy of an intervention for the exposure at population level. The PAR and PAF can be calculated using:

$$PAR = Disease\ rate\ in\ total\ population - Disease\ rate\ in\ unexposed\ group$$

and

$$PAF = \frac{Disease\ rate\ in\ total\ population - Disease\ rate\ in\ unexposed\ group}{Disease\ rate\ in\ total\ population} . \quad (5.1)$$

In this thesis the main objective was to find PAF. Levin [237] first defined the unadjusted PAF in terms of prevalence of exposure in the entire population (EP) and relative risk of disease associated with exposure (RR):

$$Unadjusted\ PAF = \frac{EP(RR-1)}{EP(RR-1)+1} .$$

The unadjusted PAF only takes into account the exposure and does not adjust for other risk factors or confounders. Given the relationship between many risk factors for dementia it would be unrealistic to expect the unadjusted PAF to give accurate results [238]. Panayatou et al. [239] and Miettinen [235] first defined the adjusted PAF. Bruzzi et al. [240] give a full derivation of the unadjusted and adjusted PAF equations. Greenland and Drescher express the same equations using vectors as follows [234]. If there are K covariates in a risk model (including but not limited to exposures and confounders), then there would be J distinct covariate patterns where $J = 2^K$ if all covariates are binary. Each participant in the sample would have one of these covariate patterns. Let $\boldsymbol{x}_1, \ldots, \boldsymbol{x}_J$ be J distinct vectors that each hold one of the J distinct covariate patterns. All these vectors will have K rows, one row for each covariate. Then $\boldsymbol{z}_1, \ldots, \boldsymbol{z}_J$ are another J vectors, again with K rows, not necessarily distinct from $\boldsymbol{x}_j$. If a participant has actual covariate pattern $\boldsymbol{x}_j$ then $\boldsymbol{z}_j$ would be the corresponding covariate pattern the participant would have if they were unexposed. Therefore

$$PAF = 1 - \boldsymbol{p}'\boldsymbol{s}. \quad (5.2)$$

Where vectors $\boldsymbol{p}$ and $\boldsymbol{s}$ both have J columns with elements

$$p_j = \Pr(\boldsymbol{x}_j | d_j = 1) \text{ and } s_j = \frac{\Pr(d_j=1 \,|\boldsymbol{z}_j)}{\Pr(d_j=1|\boldsymbol{x}_j)}$$

respectively. d_j is a binary disease indicator (prevalent or incident depending on model) and $d_j = 1$ indicates occurrence of disease whereas $d_j = 0$ indicates no disease. Therefore p_j is the covariate pattern if disease occurs and s_j is inverse relative risk for having covariate pattern $\boldsymbol{x}_j$ in comparison to covariate pattern $\boldsymbol{z}_j$. Appendix A2 has a full work through from Equation (5.1) to Equation (5.2) using methods from Bruzzi et al. [240]. Equation 5.2 can be used to estimate unadjusted and adjusted PAF, for more details see appendix A2.

Equation 5.2 produces internally valid results. If exposure prevalence and relative risk come from different sources then instead of equation 5.2, to adjust for different exposures the unadjusted PAF has to be weighted [38]:

$$Adjusted\ PAF = w \times \frac{EP(RR-1)}{EP(RR-1)+1}\ .$$

Where the weight w is uniqueness of a risk factor and can be found by using principal component analysis on a correlation matrix of all the risk factors.

5.4 Comparison of dementia PAF between CFAS I and CFAS II

5.4.1 Method

As with the relative risk analysis from the previous chapter MRC CFAS was restricted to CFAS I centres for comparison analysis with CFAS II. CFAS I and CFAS II are fully described in Chapter 2. The use of CFAS I and CFAS II allows the PAF to be adjusted for other risk factors and confounders internally. Those who died between baseline and two year follow up were excluded from this analysis, this is discussed further later in the chapter. Again, the CFAS I and CFAS II 100 dementia imputed datasets were used for analysis [6].

5.4.1.1 Comparison analysis measures from CFAS I and CFAS II

The previous chapter highlighted important risk factors for PAF analysis. Age and sex in CFAS I and age, sex, and place of residence (community, assisted living facilities, long term care) in CFAS II were known for all participants at baseline. All health conditions were self-reported variables recorded as binary for either having or not having the health condition. In the comparison analysis health conditions included transient ischaemic attack, stroke, fits/epilepsy, headaches, Parkinson's disease, anaemia and visual impairment. Other self-reported risk factors in the comparison analysis were: education (≤9, 10-11, ≥12 years), social class (skilled, semi-skilled, unskilled), place of residence (in the community, in semi-dependent housing or in care settings), marital status (married, single/divorced, or widowed), self-perceived health (excellent, good, fair, poor), feelings of loneliness (lonely or not lonely), smoking (never, quit at least 5 years ago, present and recently quit smokers), and alcohol intake (never or ever had a drink in CFAS I, 5+ days a week, 1-4 days a week, 1-4 times in 2 months, 0-2 times a year in CFAS II). Functional impairment was determined by questions from the modified Townsend Score that asked about activities of daily living and instrumental activities of daily living [89]. Item non-response for these variables was between 0.1% for place of residence and 3.2% for social class in CFAS I. Loneliness was measured at the assessment interview so by design missing data had to exceed 80%, and was 82.4%. Item non-response was between 0.5% for education and 14.8% for headaches in CFAS II. For full details on missingness see Chapter 2.

5.4.1.2 Statistical methods

The PAF is a percentage and therefore the lower bound for PAF is zero. To calculate the PAF, relative risk has to be greater than or equal to one, otherwise a negative PAF will occur. Some risk factors had to be rearranged for this to be the case. For instance, instead of lower education being the reference category with higher education being a protective factor against dementia, the reference category for education was higher education with lower education being a risk factor for dementia. To allow comparison between CFAS I and CFAS II the reference category for risk factors had to be the same. The reference categories needed for the age and sex adjusted

PAF analysis in CFAS II were prioritised and used for the CFAS I analysis, meaning that a PAF estimate was not always possible in CFAS I if the RR was less than one.

In Stata PAF is estimated after an incident risk model using the command 'punaf' [241]. The risk models have been described fully in the previous chapter. Briefly, Poisson regression models were used to estimate relative risk, inverse probability weighted for oversampling of those aged 75 years or more, sex, age, deprivation, and long term care attendance (CFAS II only). The outcome was dementia incidence after two years follow up, and risk factors were measured at baseline. Person-years for someone with incident dementia were halfway between baseline interview and two-year follow-up interview, and if dementia did not develop, the full time between interviews. Risk factors were imputed once for item non-response within each of the dementia imputations then individuals with dementia at baseline were excluded from analysis. The 'punaf' command calculates PAF based on these incident risk models using the Greenland and Drescher method from section 5.3 [234] but cannot be used after analysis with multiple imputation. In order to use the multiple imputations for PAF analysis the Poisson regression coefficient estimates and variance estimates were saved after the same model was carried out in each imputation. These estimates were combined using Rubin's rules – by finding the mean across imputations of the coefficient estimates and variance estimates. The mean across imputations was then used to calculate the PAF and confidence intervals from the same coding in Stata as in the 'punaf' command, which can be found in the command 'ado' file.

PAF analysis was first unadjusted for any other risk factors and then age and sex adjusted. Several combined models of PAF were considered. All combined models were adjusted for age and sex but age and sex were not included in the combined PAF as they are non-modifiable. Model 1 was an early to midlife model including education and occupation. Model 2 was a health condition model including transient ischaemic attack, stroke, fits/epilepsy, headaches, Parkinson's disease, anaemia, and visual impairment. Model 3 was a proximal model that included marital status, place of residence, self-perceived health, functional impairment, loneliness, smoking, and alcohol intake. Lastly Model 4 was a fully adjusted model that included all risk factors in the early to midlife model, health condition model and proximal model.

Table 5.1: Risk factors included in each of the combined models. Each model is analysed unadjusted for age and sex and adjusted for age and sex.

	Risk factors included in model	**Risk factors included in combined PAF**	**Reference categories of risk factors for ALL combined models**
Model 1	• Education • Occupation	• Education • Occupation	Age group: 65-69 years Sex: Men Education: ≥ 12 years Social class: Skilled ALL health conditions: No report of health condition Marital status: Married Place of residence: Community Self-perceived health: Excellent Functional impairment: None Loneliness: Not lonely Smoking: Never Alcohol intake: Ever in CFAS I, once to four times in two months in CFAS II
Model 2	• Transient ischaemic attack • Stroke • Fits/epilepsy • Headaches • Parkinson's disease • Anaemia • Visual impairment	• Transient ischaemic attack • Stroke • Fits/epilepsy • Headaches • Parkinson's disease • Anaemia • Visual impairment	
Model 3a	• Marital status • Place of residence • Self-perceived health • Functional impairment • Loneliness • Smoking • Alcohol intake	• Marital status • Place of residence • Self-perceived health • Functional impairment • Loneliness • Smoking • Alcohol intake	
Model 3b	Same as Model 3a	• Self-perceived health • Loneliness • Smoking • Alcohol intake	
Model 4a	All risk factors in Model 1, 2 and 3a	All risk factors included in combined PAF for Models 1, 2 and 3a	
Model 4b	Same as Model 4a	All risk factors included in combined PAF for Models 1, 2 and 3b	

Place of residence and functional impairment are closely associated with dementia and both are considered non-modifiable, along with marital status, age and sex. Therefore, the combined PAF was calculated twice for the proximal model (Model 3) and twice for the fully adjusted model (Model 4). First place of residence, functional impairment, and marital status were included in the combined PAF (Model 3a and Model 4a). Secondly, as with age and sex they were included in the model as confounders to adjust estimates but were not included in the combined PAF (Model 3b and Model 4b). Table 5.1 gives a summary of the combined PAF models. For the combined models the reference categories of the risk factors had to remain the same otherwise estimates

could not be compared between CFAS I and CFAS II. For a summary of the reference categories see Table 5.1.

5.4.2 Results

In CFAS I, there were 7635 participants at baseline, of whom 60.8% were women and the average age was 75.6 years. In CFAS II 7762 individuals participated at baseline, 56.1% were women and average age was 76.4 years. Dementia incidence at the two year follow up interview was 20.0 in CFAS I and 17.7 in CFAS II per 1000 person years as reported previously [6]. Age and sex both had a high PAF but are not modifiable so were not focused on here.

5.4.2.1 Early life risk factors

Table 5.2 gives the unadjusted estimates for early life risk factors. Although the proportion of people with low education declined between CFAS I and CFAS II, less than 9 years of education was associated with more incident dementia cases in CFAS II compared to CFAS I (Table 5.2) as risk of dementia from low education increased between the two studies. Having a semi-skilled occupation or unskilled occupation was also associated with more incident dementia cases in CFAS II compared to CFAS I (Table 5.2). Occupation level remained similar between CFAS I and CFAS II but risk increased for semi-skilled and unskilled occupations in comparison to skilled occupations. After adjusting for age and sex the PAF of dementia for education decreases instead of increases from CFAS I to CFAS II as the risk association in CFAS II is not as pronounced (Table 5.3). When adjusted for age and sex, unskilled occupation PAF still increased between CFAS I and CFAS II but PAF for semi-skilled occupation was similar (Table 5.3).

Unadjusted for age and sex the early to midlife model (Model 1) of education and occupation together was associated with 25.7% (95% CI: 0 – 59.2) of incident dementia cases in CFAS I and 36.6% (95% CI: 4.8 – 57.8) in CFAS II. Adjusted for age and sex the early to midlife model was associated with 31.5% (95% CI: 0 – 62.3) of incident dementia cases in CFAS I and with 25.6% (95% CI: 0 – 50.6) of incident dementia cases in CFAS II (Figure 5.1).

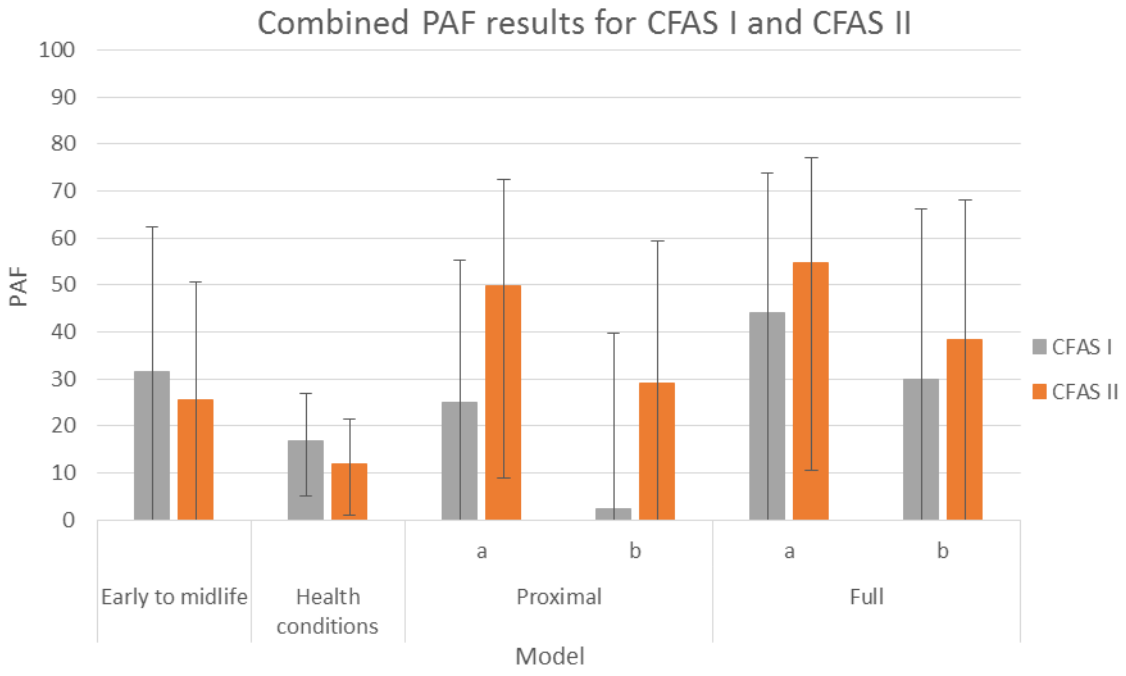
Table 5.2: Unadjusted population attributable fraction of dementia for demographic and early/midlife risk factors in CFAS I and CFAS II. NA if relative risk was less than 1 and PAF could not be calculated. Ref for reference category.

		CFAS I		CFAS II	
		PAF	95% CI	PAF	95% CI
Age Group	65-69	ref	-	ref	-
	70-74	2.3	0 – 10.7	3.8	0 – 9.4
	75-79	9.3	1.1 – 16.8	14.0	6.7 – 20.6
	80-84	24.1	13.7 – 33.3	26.0	18.2 – 33.1
	85-89	14.0	7.0 – 20.6	16.9	10.2 – 23.1
	≥90	9.6	3.9 – 14.9	11.8	5.8 – 17.5
Sex	Men	1.7	0 – 14.8	ref	-
	Women	ref	-	18.6	1.4 – 32.8
Education	≤9	22.3	0 – 51.4	33.0	20.1 – 43.7
	10-11	1.2	0 – 10.6	NA	
	≥12	ref	-	ref	-
Social Class	Skilled	ref	-	ref	-
	Semi-skilled	6.8	0 – 23.7	11.3	0 – 27.1
	Unskilled	4.7	0 – 13.5	14.7	4.4 – 23.8

Table 5.3: Population attributable fraction of dementia for demographic and early life risk factors in CFAS I and CFAS II, sex adjusted for age and other risk factors adjusted for age and sex. Ref for reference category.

		CFAS I		CFAS II	
		PAF	95% CI	PAF	95% CI
Age Group	65-69	ref	-	ref	-
	70-74	2.3	0 – 10.7	3.8	0 – 9.4
	75-79	9.3	1.1 – 16.8	14.0	6.7 – 20.6
	80-84	24.1	13.7 – 33.3	26.0	18.2 – 33.1
	85-89	14.0	7.0 – 20.6	16.9	10.2 – 23.1
	≥90	9.6	3.9 – 14.9	11.8	5.8 – 17.5
Sex	Men	9.7	0 – 22.0	ref	-
	Women	ref	-	10.8	0 – 26.4
Education	≤9	26.2	0 – 53.7	17.2	0 – 32.6
	10-11	3.2	0 – 11.8	3.9	0 – 17.5
	≥12	ref	-	ref	-
Social Class	Skilled	ref	-	ref	-
	Semi-skilled	7.6	0 – 24.3	6.8	0 – 23.9
	Unskilled	4.3	0 – 13.3	12.0	1.0 – 21.8

Figure 5.1: Population attributable fractions for combined models adjusted for age and sex. Early to midlife (education and occupation) Model 1. Health conditions (transient ischaemic attack, stroke, fits/epilepsy, headaches, Parkinson's disease, anaemia and visual impairment) Model 2. Proximal Models 3a (marital status, place of residence, self-perceived health, functional impairment, loneliness, smoking and alcohol intake) and 3b (self-perceived health, loneliness, smoking and alcohol intake). Full Models 4a (all variables from Models 1, 2 and 3a) and 4b (all variables from Models 1, 2 and 3b).



5.4.2.2 Health conditions

Unadjusted PAF estimates for health conditions are in Table 5.4. In CFAS I, out of all the health conditions, visual impairment was associated with the highest percentage of incident dementia cases (Table 5.4). This was also the case in CFAS II although not to the same extent. Stroke was associated with a similar percentage of incident dementia cases in CFAS I and CFAS II (Table 5.4). Transient ischaemic attack was associated with a greater percentage of incident dementia cases in CFAS I than in CFAS II (Table 5.4). All other health conditions were associated with a similar percentage of incident dementia cases in both studies (Table 5.4). When adjusted for age and sex both visual impairment and transient ischaemic attacks were still associated with a greater

percentage of incident dementia cases in CFAS I than in CFAS II (Table 5.5). All other health conditions were associated with similar percentages of incident dementia cases in both CFAS I and CFAS II.

Unadjusted, all health conditions considered together (Model 2) were associated with 21.2% (95% CI: 10.9 – 30.2) of incident dementia cases in CFAS I and 15.5% (95% CI: 5.7 – 24.3) in CFAS II. All health condition risk factors together were associated with 16.7% (95% CI: 5.2 – 26.8) of incident dementia cases in CFAS I after adjustment for age and sex (Figure 5.1). All health conditions combined in CFAS II were associated with 11.9% (95% CI: 1.1 – 21.5) of incident dementia cases after adjustment for age and sex (Figure 5.1).

Table 5.4: Unadjusted population attributable fraction of dementia for health condition risk factors in CFAS I and CFAS II.

	CFAS I		**CFAS II**	
	PAF	95% CI	PAF	95% CI
Transient ischaemic attack	5.4	0 – 12.2	2.0	0 – 6.6
Stroke	4.5	0 – 9.3	5.8	0.6 – 10.7
Fits/epilepsy	0.3	0 – 2.6	0.8	0 – 3.0
Headaches	1.1	0 – 6.5	2.4	0 – 8.0
Parkinson's disease	1.6	0 – 3.7	1.2	0 – 3.0
Anaemia	0.2	0 – 2.8	2.1	0 – 5.2
Visual impairment	16.2	8.1 – 23.6	6.5	0 – 13.1

Table 5.5: Population attributable fraction of dementia for health condition risk factors in CFAS I and CFAS II, adjusted for age and sex. NA if relative risk was less than 1 and PAF could not be calculated.

	CFAS I		**CFAS II**	
	PAF	95% CI	PAF	95% CI
Transient ischaemic attack	5.7	0 – 12.6	1.9	0 – 6.5
Stroke	3.4	0 – 8.3	4.1	0 – 9.2
Fits/epilepsy	0.5	0 – 2.8	1.1	0 – 3.3
Headaches	1.3	0 – 6.8	3.8	0 – 9.4
Parkinson's disease	1.4	0 – 3.6	1.2	0 – 3.1
Anaemia	NA		1.5	0 – 4.7
Visual impairment	10.4	1.3 – 18.6	2.2	0 – 9.3

5.4.2.3 Proximal risk factors

Unadjusted estimates of dementia PAF for proximal risk factors are in Table 5.6. Incident cases of dementia associated with being widowed increased between CFAS I and CFAS II (Table 5.6). In CFAS I long term care was associated with more incident dementia cases than assisted living facilities, but the opposite was true in CFAS II (Table 5.6). PAF was similar for self-perceived health between CFAS I and CFAS II (Table 5.6). Incident dementia cases associated with mild/moderate functional impairment and severe functional impairment were similarly high in CFAS I and CFAS II (Table 5.6). PAF for loneliness associated with incident dementia cases was also similar in CFAS I and CFAS II (Table 5.6). Unadjusted PAF for smoking could not be analysed in CFAS I with the reference category needed for age and sex adjusted PAF estimates but past smoking was associated with a low percentage of incident dementia cases in CFAS II (Table 5.6). Little alcohol consumption (0-2 times a year) had a high PAF in CFAS II but this was not apparent in CFAS I (Table 5.6). PAF of dementia estimates for proximal risk factors adjusted for age and sex are shown in Table 5.7. The PAF of dementia for place of residence, being widowed, self-perceived health, and loneliness was attenuated after adjustment for age and sex (Table 5.7). Smoking had a low PAF of incident dementia in CFAS II and again could not be analysed in CFAS I (Table 5.7). The PAF of dementia for drinking little was still high after adjustment, but was still not apparent in CFAS I (Table 5.7).

The combined PAF for the proximal model was calculated twice. Once including marital status, place of residence, and functional impairment in the combined PAF (Model 3a), and once adjusting for them in the model but excluding them from the combined PAF (Model 3b). Unadjusted for age and sex Model 3a was associated with 35.2% (95% CI: 0 – 60.2) of incident dementia cases in CFAS I and 59.7% (95% CI: 27.4 – 77.6) in CFAS II. Combined PAF for Model 3b unadjusted for age and sex could not be estimated as overall risk of dementia from the remaining risk factors (self-perceived health, loneliness, smoking and alcohol intake) was below one when ordered with the same reference categories as in Table 5.1. Combined PAF for Model 3b unadjusted for age and sex in CFAS II was associated with 25.0% (95% CI: 0 – 57.0) of incident dementia cases. Figure 5.1 gives Model 3a and Model 3b estimates adjusted for age and sex.

Model 3a in CFAS I was associated with 25.1% (95% CI: 0 – 55.3) of incident dementia cases. In CFAS II, Model 3a was associated 49.9% (95% CI: 8.9 – 72.5) of incident dementia cases. Model 3b was associated with 2.4% (95% CI: 0 – 39.6) of incident dementia cases in CFAS I, 29.1% (95% CI: 0 – 59.3) of incident dementia cases were associated with Model 3b in CFAS II.

Table 5.6: Unadjusted population attributable fraction of dementia for proximal risk factors in CFAS I and CFAS II. Alcohol intake measured differently in CFAS I and CFAS II. NA if relative risk was less than 1 and PAF could not be calculated. Ref for reference category.

		CFAS I		**CFAS II**	
		PAF	95% CI	PAF	95% CI
Marital Status	Married	ref	-	ref	-
	Single/divorced	3.4	0 – 9.1	4.4	0 – 9.9
	Widowed	24.1	9.7 – 36.3	35.9	24.5 – 45.7
Place of residence	Community	ref	-	ref	-
	Assisted living facilities	4.7	0 – 10.0	10.3	4.4 – 16.0
	Long term care	9.0	4.2 – 13.6	4.8	1.2 – 8.3
Self-perceived health	Excellent	ref	-	ref	-
	Good	7.5	0 – 25.8	8.1	0 – 24.3
	Fair	10.2	0 – 21.6	13.4	2.4 – 23.2
	Poor	5.6	0.4 – 10.4	3.4	0 – 7.5
Functional Impairment	None	ref	-	ref	-
	Mild/moderate	7.4	0.7 – 13.7	11.5	3.0 – 19.4
	Severe	26.3	18.0 – 33.8	23.8	15.7 – 31.1
Loneliness	Not lonely	ref	-	ref	-
	Lonely	10.1	0 – 21.9	11.2	3.0 – 18.7
Smoking	Never	ref	-	ref	-
	Past	NA		3.0	0 – 17.1
	Current	NA		NA	
Alcohol intake	Ever	ref	-	.	.
	Never	2.4	0 – 8.1	.	.
	5 or more days a week	.	.	2.3	0 – 9.1
	1-4 days a week	.	.	ref	-
	1-4 times in 2 months	.	.	4.1	0 – 10.5
	0-2 times a year	.	.	34.0	21.5 – 44.6

Table 5.7: Population attributable fraction of dementia for proximal risk factors in CFAS I and CFAS II, adjusted for age and sex. Alcohol intake measured differently in CFAS I and CFAS II. NA if relative risk was less than 1 and PAF could not be calculated. Ref for reference category.

		CFAS I		CFAS II	
		PAF	95% CI	PAF	95% CI
Marital Status	Married	ref	-	ref	-
	Single/divorced	1.5	0 – 7.5	3.7	0 – 9.2
	Widowed	8.2	0 – 25.1	20.5	4.6 – 33.7
Place of residence	Community	ref	-	ref	-
	Assisted living facilities	1.2	0 – 6.8	6.8	0.4 – 12.8
	Long term care	7.0	1.9 – 11.9	4.4	0.6 – 8.1
Self-perceived health	Excellent	-	-	-	-
	Good	7.6	0 – 25.9	3.8	0 – 21.5
	Fair	9.3	0 – 20.9	9.4	0 – 20.3
	Poor	5.7	0.6 – 10.6	3.2	0 – 7.4
Functional Impairment	None	ref	-	ref	-
	Mild/moderate	3.6	0 – 10.5	3.2	0 – 12.6
	Severe	20.2	10.3 – 29.0	18.4	9.4 – 26.5
Loneliness	Not lonely	ref	-	ref	-
	Lonely	8.2	0 – 20.3	6.8	0 – 14.7
Smoking	Never	ref	-	ref	-
	Past	NA		3.8	0 – 18.3
	Current	NA		4.4	0 – 10.1
Alcohol intake	Ever	ref	-	.	.
	Never	0.6	0 – 6.4	.	.
	5 or more days a week	.	.	NA	
	1-4 days a week	.	.	ref	-
	1-4 times in 2 months	.	.	1.7	0 – 8.6
	0-2 times a year	.	.	26.8	11.9 – 39.1

5.4.2.4 Fully adjusted PAF

The fully adjusted combined PAF was also calculated twice. Once including marital status, place of residence, and functional impairment in the combined PAF (Model 4a), and once adjusting for these risk factors but excluding them from the combined PAF (Model 4b). In CFAS I Model 4a was associated with 50.8% (95% CI: 0 – 77.2) of incident dementia cases and in CFAS II was associated with 62.9% (95% CI: 26.9 – 81.2) unadjusted for age and sex. Model 4b unadjusted for age and sex was associated with 24.2% (95% CI: 0 – 64.0) of incident dementia cases in CFAS I and 39.1% (95% CI: 0 – 68.6) in CFAS II. Figure 5.1 gives the combined estimates for Model 4a and Model 4b adjusted for age and sex. In CFAS I Model 4a was associated with 44.2% (95% CI: 0 – 73.9) of incident dementia cases whereas in CFAS II Model 4a was associated with 54.8% (95% CI: 10.4 –

77.2) of incident dementia cases. Model 4b in CFAS I was associated with 29.9% (95% CI: 0 – 66.2) of incident dementia cases whilst in CFAS II was associated with 38.3% (95% CI: 0 – 68.0) of incident dementia cases.

5.5 CFAS II risk factors only PAF analysis

5.5.1 Method

As mentioned in section 4.4 there were some risk factors available in CFAS II that were not available in CFAS I. The same imputed datasets as from section 4.4.1 were used to complete a separate PAF analysis in CFAS II with different risk factors indicated as associated with incident dementia (section 4.4.2). These included deprivation (measured using the Townsend deprivation index and then split into tertiles [84]), hypotension, head injury and physical inactivity. As transient ischaemic attack and visual impairment were included in the PAF comparison analysis because they increased risk only in CFAS I, they were excluded from this analysis – the individual PAF and the combined models. PAF was calculated using methods in section 5.3. Hypotension and head injury were included in the health condition combined model. Deprivation and physical inactivity were added to the proximal models. Hypotension, head injury, deprivation and physical inactivity were included in the fully adjusted models. As in Table 5.1 the reference category in the combined models for hypotension and head injury was no report of health condition. The reference category in all combined models for deprivation was least deprived and for physical inactivity was physically active.

5.5.2 Results

Estimates for the unadjusted and age and sex adjusted CFAS II only PAF analysis are in Tables 5.8, 5.9 and 5.10. Hypotension and head injury were associated with a modest percentage of incident dementia cases (Table 5.9). Deprivation and physical inactivity were both highlighted as important risk factors for dementia (Table 5.10). When adjusted for age and sex PAF for

hypotension and head injury were similar to when unadjusted (Table 5.9). Deprivation and physical inactivity remained important risk factors for incident dementia after adjustment for age and sex (Table 5.10).

Table 5.8: Unadjusted and age and sex adjusted PAF using 20 imputed datasets where dementia and risk factors were imputed together in CFAS II, demographic and early to midlife risk factors. Ref for reference category.

		Unadjusted		**Age and sex adjusted**	
		PAF	95% CI	PAF	95% CI
Age Group	65-69	ref	-	ref	-
	70-74	4.5	0 – 10.2	4.5	0 – 10.2
	75-79	14.4	7.6 – 20.7	14.4	7.6 – 20.7
	80-84	26.1	17.5 – 33.8	26.1	17.5 – 33.8
	85-89	18.3	11.6 – 24.5	18.3	11.6 – 24.5
	≥90	11.7	6.3 – 16.8	11.7	6.3 – 16.8
Sex	Men	ref	-	ref	-
	Women	20.9	5.1 – 34.1	13.4	0 – 27.7
Education	≤9	38.6	26.9 – 48.4	25.6	9.6 – 38.8
	10-11	5.8	0 – 18.2	9.1	0 – 20.6
	≥12	ref	-	ref	-
Social Class	Skilled	ref	-	ref	-
	Semi-skilled	16.8	0 – 31.4	12.9	0 – 28.7
	Unskilled	19.3	10.1 – 27.5	17.0	7.0 – 25.9

Table 5.9: Unadjusted and age and sex adjusted PAF using 20 imputed datasets where dementia and risk factors were imputed together in CFAS II, health condition risk factors.

	Unadjusted		**Age and sex adjusted**	
	PAF	95% CI	PAF	95% CI
Hypotension	2.9	0 – 7.3	3.4	0 – 7.8
Stroke	7.5	1.7 – 13.0	5.8	0 – 11.5
Fits/epilepsy	1.5	0 – 3.9	1.8	0 – 4.3
Headaches	1.9	0 – 7.3	3.3	0 – 8.6
Head injury	3.1	0 – 8.9	4.5	0 – 10.3
Parkinson’s disease	2.0	0 – 4.4	2.0	0 – 4.5

Table 5.10: Unadjusted and age and sex adjusted PAF using 20 imputed datasets where dementia and risk factors were imputed together in CFAS II, proximal risk factors. NA if relative risk was less than 1 and PAF could not be calculated. Ref for reference category.

		Unadjusted		Age and sex adjusted	
		PAF	95% CI	PAF	95% CI
Marital Status	Married	ref	-	ref	-
	Single/divorced	5.2	0 – 11.4	4.6	0 – 10.8
	Widowed	40.1	30.6 – 48.4	26.1	13.1 – 37.2
Place of residence	Community	ref	-	ref	-
	Assisted living facilities	11.3	5.1 – 17.1	7.8	1.2 – 14.0
	Long term care	5.5	1.9 – 9.0	5.2	1.4 – 8.7
Deprivation tertiles	Least deprived	ref	-	ref	-
	Mid-level deprivation	11.0	0.1 – 20.7	10.3	0 – 20.1
	Most deprived	18.6	5.9 – 29.6	15.7	2.0 – 27.4
Self-perceived health	Excellent	ref	-	ref	-
	Good	4.2	0 – 21.5	NA	
	Fair	15.4	3.7 – 25.7	11.2	0 – 22.9
	Poor	4.7	0 – 9.5	4.5	0 – 9.3
Functional Impairment	None	ref	-	ref	-
	Mild/moderate	13.0	5.0 – 20.3	6.1	0 – 15.0
	Severe	30.4	22.8 – 37.2	26.0	17.6 – 33.6
Loneliness	Not lonely	ref	-	ref	-
	Lonely	14.9	7.0 – 22.2	10.6	2.2 – 18.3
Smoking	Never	ref	-	ref	-
	Past	4.3	0 – 18.0	5.8	0 – 19.5
	Current	1.5	0 – 8.0	6.1	0 – 12.0
Alcohol intake	5 or more days a week	0.7	0 – 6.4	NA	
	1-4 days a week	ref	-	ref	-
	1-4 times in 2 months	4.6	0 – 11.1	2.5	0 – 9.4
	0-2 times a year	41.8	28.9 – 52.4	35.6	20.2 – 48.0
Physical inactivity	Active	ref	-	ref	-
	Inactive	14.1	8.4 – 19.4	12.0	6.0 – 17.5

5.6 Discussion

PAF for dementia changed over time. The largest temporal differences in PAF after adjustment for age and sex for individual risk factors were for education, social class, marital status and visual impairment. There was a slight increase from CFAS I to CFAS II in the age and sex adjusted fully combined PAF that included education, occupation, transient ischaemic attack, stroke, fits/epilepsy, headaches, Parkinson's disease, anaemia, visual impairment, self-perceived health, loneliness, smoking and alcohol intake. This was mainly because of the increase in incident dementia associated with proximal risk factors such as loneliness, smoking and alcohol intake.

Combined PAF for the early/midlife model that included education and occupation and the combined PAF for the health conditions model that included transient ischaemic attack, stroke, fits/epilepsy, headaches, Parkinson's disease, anaemia and visual impairment were similar in both studies.

5.6.1 Strengths and limitations

These findings were from two large population based studies that randomly sampled from three different areas across rural and urban settings to be representative of the UK. The interviews for CFAS I and CFAS II included many health, socio-demographic, and lifestyle factors, enabling a broad range of risk factors to be studied for PAF at two time points. The individual and combined PAF could be adjusted for other risk factors and confounders. The sampling method and study dementia diagnosis remained constant between the two studies, meaning that changes in PAF between CFAS I and CFAS II were not due to changes in study sampling or diagnostic criteria. However there were some limitations. Response rate declined between CFAS I and CFAS II (fully discussed in Chapter 2), this is a common problem amongst other studies and this analysis used inverse probability weights to ensure population representativeness [93]. Those who died between baseline and two-year follow-up interview were excluded from this analysis. As shown in Chapter 3 those with cognitive impairment/dementia and some of the risk factors (such as education, functional impairment and smoking) were at increased risk of death. This could mean that estimates of dementia risk are conservative which in turn would impact estimates of PAF. Evidence suggests that cardiovascular risk factors in midlife rather than in later life increase dementia risk. In both CFAS I and CFAS II participants were aged 65 years and above so could not determine midlife risk factors for dementia. There was no evidence of increased risk of dementia from later life diabetes or hypertension in either CFAS I or CFAS II so these were not included in the PAF analysis. Follow up for incident dementia was only two years which could put direction of association between risk factor and dementia under question, especially for place of residence and functional impairment. However, a short follow up period means that risk factor status is less likely to change between measurement and follow up. Confidence intervals for PAF were wide, the lower bound for many was negative and was restricted to zero in the tables as a negative PAF is not interpretable. As confidence intervals are wide, results should be interpreted with caution and not viewed as conclusive evidence.

5.6.1.1 Strengths and limitations of PAF as a measure

The PAF is a particularly useful measure as it can help to determine which risk factors should be targeted at a population level to prevent dementia. However, there are limitations to the PAF measure. Causality has to be assumed when estimating the relative risk, but it is usually incorrect to assume that the PAF measures the proportion of disease caused by a risk factor. The cause of disease is often a mixture of many different health and lifestyle factors and trying to pinpoint one cause of a disease is inappropriate. Although the best way to infer causality is through clinical trials, in many cases this would not be possible (for instance health conditions) or ethical (for instance smoking and alcohol intake). Therefore estimates from reliable observational studies are needed. The PAF estimates the proportion or percentage of disease associated with a risk factor and as each disease case can be associated with many different risk factors, these will overlap. Single risk factor PAF estimates will be optimistic as many individuals who develop dementia with one particular risk will also have been exposed to many other risk factors. Even if it was possible to completely eliminate a risk factor this would not necessarily mean that dementia cases would be prevented and eliminating one risk factor would impact the other risk factors and mortality. The PAF is bounded at the lower end by zero and cannot be estimated when a relative risk is less than or equal to one, therefore risk factors were chosen from Chapter 4 that increased risk of dementia or were protective factors that could be rearranged to be risk factors for dementia. A comparison of PAF between unadjusted and adjusted models or between CFAS I and CFAS II was not always possible if reference category needed to estimate PAF differed between analyses.

5.6.2 Interpretation of results

5.6.2.1 Individual risk factor PAF

Previous results for individual PAF in the UK differ to the ones here. Previously unadjusted PAF was estimated at 12.2% for low education, 10.6% for smoking and 21.8% for physical inactivity [38]. In CFAS II unadjusted PAF for education was 33.0%, past smoking 3.0% and physical inactivity 14.9%. The differences in PAF are likely due to differences in definition of the risk

factors. In Norton et al. low education was classified as lower secondary schooling or less and smoking was separated into smokers and non-smokers (binary measures) [38]. Here education was split into ≤9 years education, 10-11 years of education and ≥12 years education and smoking into never, past and current smokers. Physical inactivity was defined as either 20 minutes of vigorous activity at least 3 days a week or 30 minutes of moderate activity on 5 or more days a week in Norton et al. whereas here physical inactivity was defined as not participating in low, moderate or vigorous physical activity. Although PAF results differ for these three risk factors the conclusions are the same, that low education, smoking and physical inactivity account for a substantial percentage of incident dementia cases.

A previous study found that there was an increase in the PAF over time for hypertension but that PAF for diabetes, past smoking and low education remained similar [49]. Hypertension and diabetes were not analysed for PAF here and age and sex adjusted PAF for smoking could not be compared. Age and sex adjusted PAF for low education declined from CFAS I to CFAS II. Low education is defined the same way in the Netherlands [49] as in CFAS I and CFAS II but the decrease in the percentage of people with low education was not as marked. Also, individual education PAF was adjusted for more than just age and sex in de Bruijn et al. [49].

5.6.2.2 Combined PAF models

Much previous work on combined PAF of dementia has been confined to only a few risk factors [173, 226-231, 242-244]. Here many socio-demographic, health, and lifestyle risk factors for dementia were included in the fully combined PAF. The combined PAF estimates the percentage of incident dementia cases associated with risk factors considered in the model so is likely to differ depending on the choice of risk factors included. A recent development in the methodology for the combined PAF has enabled dependence between risk factors to be accounted for when relative risk estimates and prevalence are from different sources [38]. Others have been able to replicate these methods for the same risk factors in their own countries [232] or to include more risk factors in the combined PAF [47] giving estimates of between 28.2% and 48.4% for combined PAF.

Here, the combined PAF for education, occupation, transient ischaemic attack, stroke, fits/epilepsy, headaches, Parkinson's disease, anaemia, visual impairment, self-perceived health, loneliness, smoking, and alcohol intake was associated with 29.9% of incident dementia cases in CFAS I and 38.3% in CFAS II. Compared to other studies that give adjusted estimates for combined PAF, these results were at the low to mid end, even though more risk factors were included. This could be because non-modifiable risk factors other than age and sex were adjusted for, including marital status, place of residence, and functional impairment [38, 47, 49, 232]. However this variation in estimates between different studies could potentially be due to different risk factor profiles between countries. Previously, the combined PAF in the UK for low education, diabetes, midlife hypertension, midlife obesity, physical inactivity, depression and smoking was 30.0%, similar to the CFAS I estimate here.

Another study found a slight increase in combined PAF over time [49]. There are limitations to the comparability of these estimates with ones from CFAS I and CFAS II as different risk factors were included in the combined PAF and the estimates were for the Netherlands, where dementia risk factor profile changes over time are likely to differ to the UK.

5.6.4 Recommendations for dementia prevention

Although there was only a slight increase in fully adjusted combined PAF between CFAS I and CFAS II, there was a large increase in the percentage of incident dementia cases associated with proximal risk factors. PAF associated with the early/midlife model and health conditions remained relatively stable in both studies. This indicates that proximal risk factors, or the fundamental risks they represent, such as loneliness and smoking have become more important in the prevention of dementia over time. Research into prevention of loneliness and social isolation suggests that group activities with an educational component are more effective compared to one to one support [245]. Increased awareness and availability of local community activities provided by local authorities and charities could help prevent loneliness. Prevalence of smoking has already decreased over time but further decreases in prevalence of smoking would still be advantageous given that people who smoke are now living long enough to experience dementia. The results for alcohol intake differed vastly between CFAS I and CFAS II. Results from CFAS I showed no association between drinking alcohol and dementia but results from CFAS II suggest drinking less

alcohol increases risk of dementia. Another study has found that alcohol use disorders increased risk of dementia by a large margin [220]. Another reason for the alcohol result seen in CFAS II could be that doctors recommend discontinuing alcohol consumption to many people with serious health conditions which may account for the high risk of dementia associated with only drinking once or twice a year. As the association between alcohol intake and dementia is unclear and alcohol is connected with many other health problems increasing alcohol intake to prevent dementia is not recommended. The results also show that early to midlife risk factors are as important now as before. Encouraging further education and occupational attainment would still help prevent dementia, as would continuing improvement in management, medication, and care of cardiovascular risk factors.

5.6.5 Conclusions

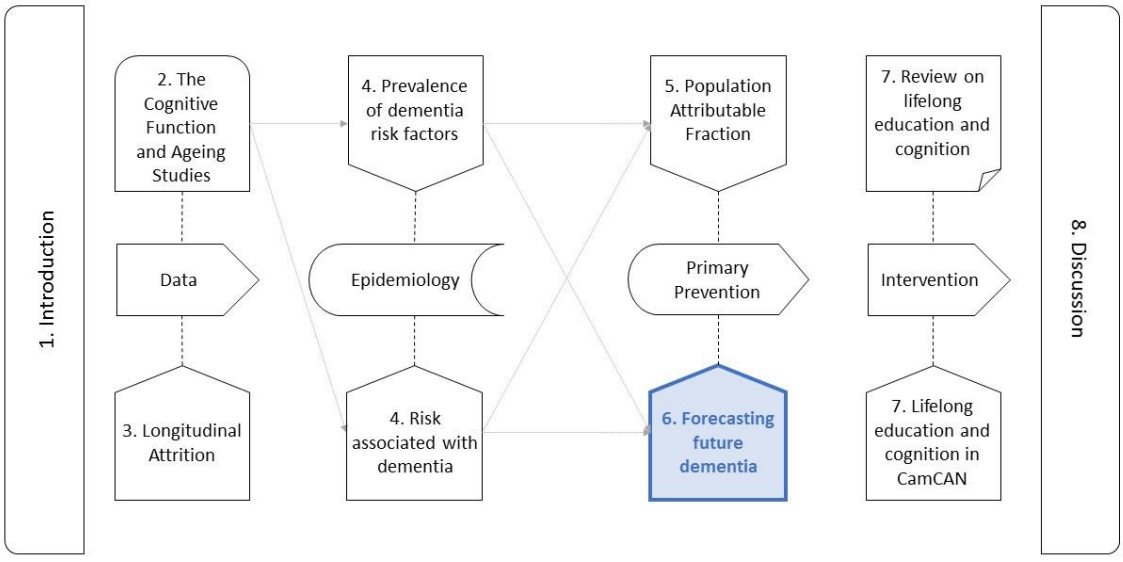
With mounting evidence suggesting that cardiovascular factors increase risk of dementia in midlife rather than later life, further research into PAF of midlife risk factors of dementia is needed. The risk factor profile of dementia differs between countries, even within high income countries, for instance midlife obesity is more prevalent in America than European countries. This will have an impact on the PAF associated with dementia and therefore more research is needed to both confirm results for the UK and also to provide estimates for other countries.

Chapter 6: Forecasting dementia

6.1 Chapter overview

The last two chapters have shown that various aspects of dementia risk have changed across time including their prevalence, risk association with dementia and the impact they have on dementia at a population level. Age specific dementia prevalence and incidence have already decreased over time, partially due to the changes seen in the risk factors over time. It is important to know how current trends in dementia risk factors might impact future dementia prevalence.

To look at the impact of cognitive impairment trends on longevity and disability, future cognitive impairment has previously been estimated using data from MRC CFAS [246].



6.2 Background

A comparison using stable methodology over time has provided evidence that age specific dementia prevalence is decreasing in the UK [7]. Other studies from Europe suggest that dementia prevalence is remaining constant or decreasing [10] as well as further afield [9, 11]. However, it is unclear whether age specific dementia prevalence will continue to decrease in the future or whether it will be offset by population ageing. Dementia presents a substantial challenge to health and social care [47], therefore estimation of future dementia numbers is essential when planning future care needs. Despite a decrease in the numbers of care beds [1, 7] demand for spaces in care settings and supported housing is expected to increase, along with cost [247, 248]. Although overall age standardised dementia prevalence in the UK has declined, dementia prevalence within care settings is increasing. The prevalence of risk and protective factors, risk associated with dementia (Chapter 4) and the impact risk factors have on dementia prevention (Chapter 5) are changing over time and therefore so will dementia itself.

6.2.1 Background on forecasting methodology

There are different ways to go about modelling future dementia. A commentary on dementia projection studies described three different methodologies from the literature [249]. Extrapolation models were the simplest, where current age group (and sometimes sex) specific dementia prevalence is multiplied by future population projections [2, 250-253]. Macro-simulation uses a multistate illness-death model to model transitions between no dementia, dementia and mortality [150, 254-261]. Equations for the multi-state models are then multiplied by age group and sex specific population projections to forecast dementia at the same time as mortality. Micro-simulation models individuals unlike macro-simulation that models groups of people. Micro-simulation can also model continuous rather than discrete time which allows dementia incidence to be more accurately estimated [4, 27, 262, 263]. Micro-simulation models of dementia also allow for competing risks of other health conditions as they model each individual who enters the model separately over their life-course. For more on the methodology of micro-simulation models see [264-266].

Although extrapolation models are the easiest to implement they are also the least accurate as unrealistic assumptions have to be made. For instance age and sex specific dementia prevalence are assumed to remain constant over time when this is unlikely to be the case. Extrapolation models also do not take into account differences in mortality between those with and without dementia or trends in risk factors of dementia over time. Macro-simulation models are able to take into account mortality differences between those with and without dementia and risk associated with dementia whilst micro-simulation models in addition take into account trends in risk factors of dementia over time.

Other methods to forecast dementia have recently been developed [37, 38, 267, 268]. The PAF has been used to adjust extrapolation models of dementia forecasts for trends in midlife obesity and mortality differences for those with and without midlife obesity [267] and separately to assess the impact of risk reduction on macro-simulation models [37, 38, 232]. Extrapolation models could also be adjusted for midlife obesity trends by calculating dementia prevalence in those with or without midlife obesity [268].

6.2.2 Dementia forecasts for the UK

Prior to this forecasting work, only extrapolation [2] and macro-simulation [38, 150] dementia forecasts have been available for the UK. More recently, results from a micro-simulation that models future dementia estimates have been released [4]. Previous projections for the UK predict that number of dementia cases will rise in the future to between 1,204,500 and 1,750,000 people with dementia in the UK by 2040 [2, 38, 150]. The micro-simulation model did not forecast to 2040 but estimated there would be 1,227,500 people with dementia in 2035 based on the future age structure and other health conditions [4]. Prevalence was also predicted to rise in the future [4, 150]. Dementia forecasts for other countries also suggest the number of people with dementia will increase over time [250-263, 268]. No dementia forecasts predict a reduction in number of dementia cases from the present day onwards, irrespective of methodology. Any that included prevalence forecasts also predicted increases in prevalence over time [255, 256, 261-263], even under scenarios delaying dementia or of risk reduction [263] or different mortality trends [255].

The micro-simulation model for the UK incorporated data from CFAS II, however, for enough data to allow micro-simulation data from Understanding Society and the English Longitudinal Study of Ageing (ELSA) were also used. Projections of cognitive impairment have previously been published using data from MRC CFAS. Future cognitive impairment estimates differed depending on inclusion of different socio-demographic and health factors and model differences [25, 246, 269].

Although micro-simulation is the optimal forecasting method, it requires large amounts of longitudinal data. Other ways to account for risk factor trends have been developed but only for a single risk factor (midlife obesity [268]). The aim of this work was to forecast future cases and prevalence of dementia accounting for trends in several risk factors and the interaction between those risk factors without extensive longitudinal data. A further aim was to see whether prevention of dementia risk factors could mitigate expected dementia cases in the future. Nepal et al. [268] detailed dementia forecasting methods that accounted for trends in obesity prevalence over time without large amounts of longitudinal data but did not consider forecasting dementia with multiple risk factor trends. Here, Nepal et al. [268] methods of forecasting are extended to include multiple risk factors. To adjust for the interaction between multiple risk factors, methods from Norton et al. [38] were implemented.

6.3 Methods

6.3.1 Data

The main datasets used in this analysis were the population based first and second Cognitive Function and Ageing Studies (CFAS I and CFAS II). All details of CFAS I and CFAS II are provided in Chapter 2. Briefly, for both CFAS I and CFAS II a random sample stratified by age (65-75 and 75+) was taken from the Family Health Service Authority lists with a 80% response rate in CFAS I and a 56% response rate in CFAS II. Baseline interviews began in 1991 for CFAS I and 2008 for CFAS II in Cambridgeshire, Nottingham and Newcastle [91]. The participant interview, two stages in CFAS I and one stage in CFAS II, included self-reported items on health, lifestyle, and cognition

incorporating Automated Geriatric Examination for Computer Assisted Technology (AGECAT) algorithm questions for a study diagnosis of dementia. If answers for the AGECAT algorithm were incomplete, a diagnostician (CB) considered information from the interviews allocating a DSM-IIIR diagnosis of dementia. A subsample including all those who were cognitively frail were asked to nominate a friend, family member or carer to take part in an informant interview.

The Health Survey for England (HSE) time series dataset from 1991-2009 [270] and the General Household Survey (GHS) time series dataset from 1972-2004 [271] were used to investigate midlife risk factor trends.

The Health Survey for England (HSE) looks at changes in health and lifestyle over time and is the main source of information on health for the Government. It started in 1991 and has continued annually since. Originally the survey was for adults aged 16 years and over but from 1995 onwards also included children aged 2 to 15 years. A multi-stage sampling design was used where first a random sample of primary sampling units (PSUs) was selected based on postcode then within the PSUs, individual addresses were chosen at random. Stratified sampling was used so that households were selected proportionally from the PSUs. Until 2014, up to 10 adults aged 16 years or more at the address were selected for interview but a maximum of 2 children between the ages of 0 and 15 years were selected. In 2015 this changed so that as many as two children aged 0 to 12 years and two children aged 13 to 15 could be selected. Response rate has been reported as between 58% and 75% for years 1994 to 2009 [272]. Response rate was not available for years 1991 to 1993, possibly because the survey was conducted by the Office of Population Censuses until 1993 and by the Joint Health Surveys Unit of the National Centre for Social Research since 1994. A letter is then sent to the chosen households with an interviewer visit within the following week to interview everyone eligible in the household. The core interview contains questions on wellbeing, social care, and lifestyle. If consent is given a qualified nurse will visit to take some measurements such as height, weight and blood pressure and will also ask what medications are being taken. Around 8,000 adults and 2,000 children take part in the survey every year. Each year there is a focus on a particular population group, disease or condition and additional questions are asked. Recently for instance there was a focus on respiratory health and lung function in the years 1999, 2000, and 2010; kidney disease in 2009 and 2010; and wellbeing in 2010 and 2011. Care and nursing homes were only included in the year 2000 sample whilst in

every other year the sample was taken only from private households. In general those living in care or nursing homes tend to be older and less healthy than those living in private households.

The GHS, now named the General Lifestyle Survey was conducted by the Office for National Statistics (ONS) and ran between 1971 and 2011 [273]. Here the time-series dataset from 1972 – 2004 was used. The GHS interviewed individuals living in private households annually on five main topics: education, employment, health, housing, and population and family information. Between 1972 and 2004 response rate was between 67% and 85% [274, 275]. The GHS was subject to five-year review and as a result other topics were covered periodically, such as leisure, smoking and alcohol consumption. Each year there was a new sample of approximately 9,000 households and 16,000 individuals from everyone living in private households in Great Britain. The sample design has always been two stages with households sampled from PSUs and then individuals sampled within the households. The sampling frame for PSUs changed in 1984 from the Electoral Registers to the Postal Address File. Once consent was given the Household Reference person or spouse would answer a household questionnaire and all adults aged 16 years or over would complete an individual questionnaire. From 2005 onwards a longitudinal design was also adopted where the sample would be followed up for four years, this was to be in line with European requirements.

6.3.2 Risk Factors

Previous work highlighted key risk factors including stroke, midlife obesity, midlife hypertension, midlife physical inactivity, midlife hearing impairment, social isolation (all binary) and smoking (current, past and never), with education (up to 9 years, 10 to 11 years and 12 or more years) as a protective factor [36, 38, 45-47]. There was no evidence in CFAS I or CFAS II of hearing impairment or social isolation (measured as frequency of seeing relatives or friends) in later life being risk factors for dementia (Chapter 4) so both were excluded. Midlife physical inactivity increased with age but remained stable for men and women across birth cohort (over time) in the relevant age range (45 to 55 years) so was excluded (Figures 6.1 and 6.2).

Figure 6.1: Physical inactivity prevalence in men by age in all birth cohorts that included any age in the age range 45-55 years from the Health Survey for England time series data. o Δ are estimates based on less than 150 observations.

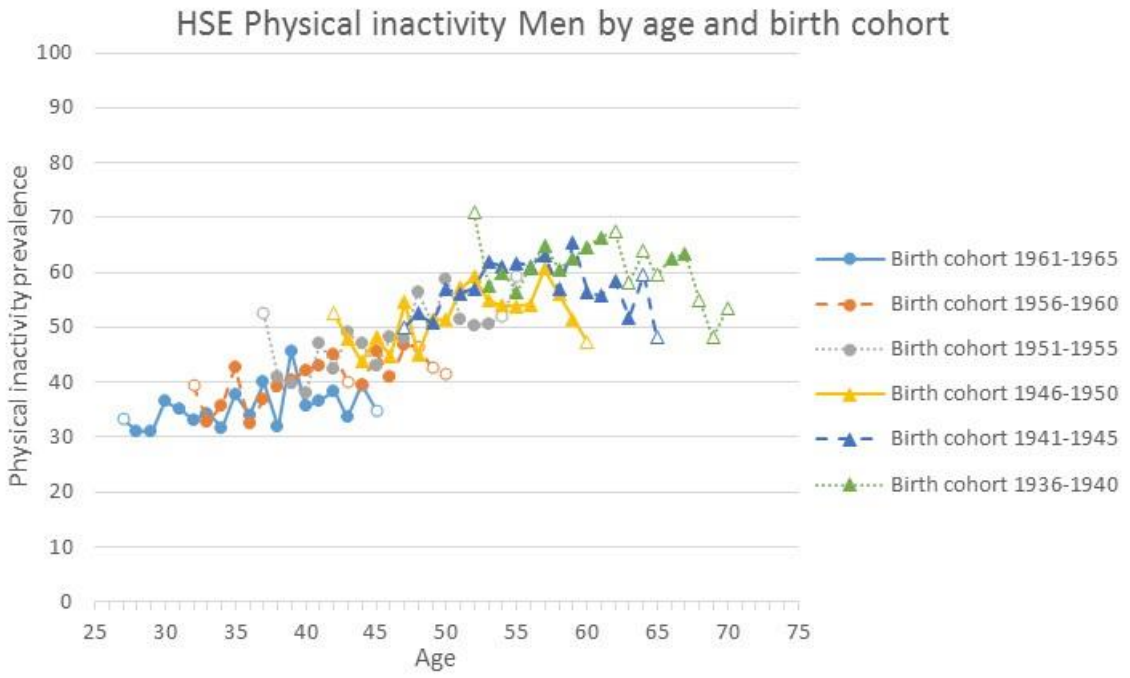
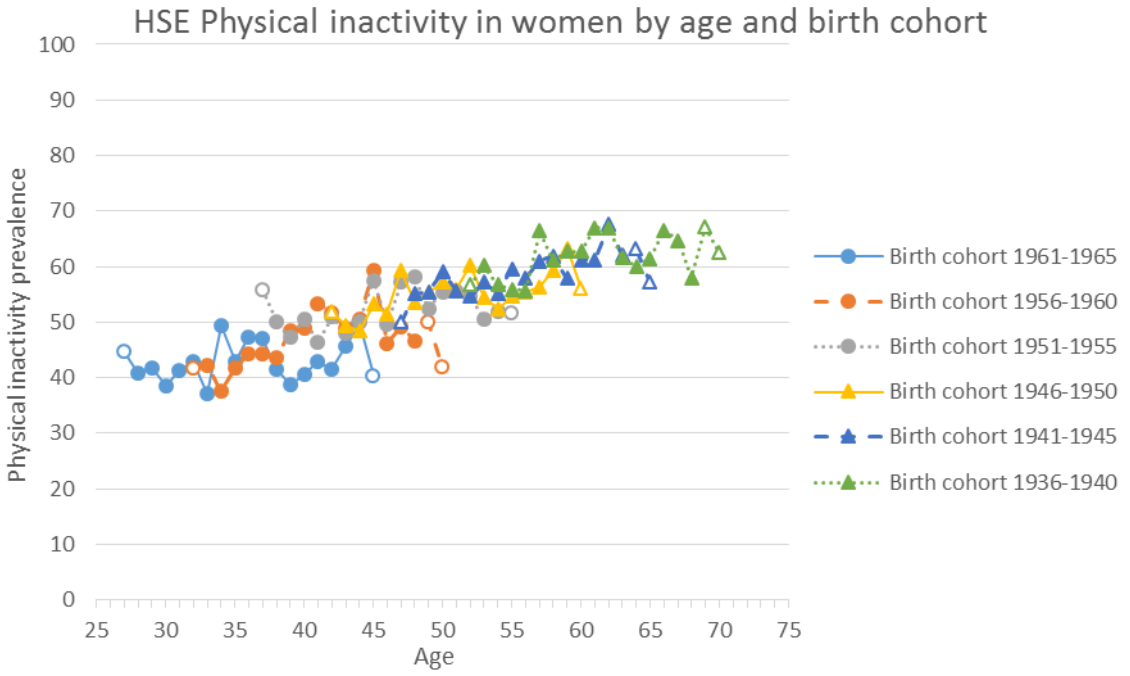


Figure 6.2: Physical inactivity prevalence in women by age in all birth cohorts that included any age in the age range 45-55 years from the Health Survey for England time series data. o Δ are estimates based on less than 150 observations.



6.3.3 Relative Risk and Risk Factor Trends

Risk of dementia from a single time point is used. Risk of dementia from smoking, stroke and education were estimated from CFAS II. Relative risk from the 100 dementia imputed datasets with risk factors imputed once within each dementia imputed dataset for CFAS II was used. For more information on the methods see section 4.3.1.3. After risk factors were imputed those with dementia at baseline were excluded. The inverse probability weights were the same as in the risk and PAF analysis and accounted for initial non-response oversampling of those aged 75 years and above, age, sex and care home residence.

All participants in CFAS II were aged 65 years or over and therefore midlife obesity risk was obtained from a systematic review [36]. A meta-analysis was conducted on four studies [276-279] to estimate midlife hypertension risk. The same review that analysed midlife obesity risk also undertook a meta-analysis on midlife hypertension risk but midlife hypertension prevalence was by measured blood pressure and therefore the meta-analysis risk also needed to be. Two studies in the midlife hypertension meta-analysis had to be excluded as the risk from midlife hypertension was not binary [280] or because midlife hypertension was measured as a combined variable of blood pressure or anti-hypertensive medicine usage [281]. Table 6.1 summarises dementia risk factors adjusted for in the forecasting model, the trend in prevalence of these risk factors over time, the origin of the estimate of dementia risk from that risk factor, the original risk estimate, uniqueness used to account for overlap between risk factors (methodology discussed later) and the adjusted risk estimate after accounting for uniqueness.

Table 6.1: Summary of dementia risk factors adjusted for in the forecasts, their prevalence trend over time, origin and estimate of relative risk used in the single factor forecasts, the uniqueness used to find the adjusted relative risk and the adjusted relative risk used in the combined forecasts

Risk factor		Prevalence trends	Relative risk from	Risk	Uniqueness	Adjusted risk
Education	≤ 9	Higher education increasing, from CFAS I & II and the GHS	CFAS II	1.0	-	1.00
	10 – 11			0.7	0.3766	0.87
	≥ 12			0.7	0.3766	0.87
Smoking	Never	Past and current smoking decreasing, from HSE	CFAS II	1.0	-	1.00
	Past			1.1	0.2774	1.03
	Current			1.5	0.2774	1.13
Stroke		Increasing, from HSE	CFAS II	1.5	0.4193	1.20
Midlife obesity		Increasing, from HSE	Meta-analysis from recent systematic review [36]	1.6	0.5219	1.30
Midlife hypertension		Decreasing, from HSE	Meta-analysis of [276-279]	1.3	0.3571	1.10

Early and midlife risk (education, midlife obesity and midlife hypertension) by definition are obtained prior to older age. Therefore status does not change in later life and prevalence trends were modelled by birth cohort. Late life risk factor status (smoking and stroke) could change after age 65 so prevalence trends were modelled by age and year.

Current and future prevalence of education by birth cohort were modelled from CFAS I, CFAS II and GHS time series data [271]. For birth cohorts 1946 onwards estimates for 9 years or less of education (less than statutory for these cohorts) were assumed to remain constant, 12 years or more of education were GHS estimates and 10 to 11 years of education was subtracted.

Midlife (45-55 years) obesity and midlife hypertension trends were modelled using HSE time series data [270]. To ensure the trend seen was over time instead of average age of the birth cohort getting younger, obesity prevalence and hypertension prevalence were plotted against age, by birth cohort. This partial data was extrapolated using a binomial log link Generalised

Linear Model for mean predicted prevalence of obesity or hypertension in the age range 45-55 years.

Estimates for birth cohorts 1916 to 1931 and 1966 to 1975 were still needed for midlife obesity and birth cohorts 1916 to 1936 and 1966 to 1975 for midlife hypertension. Obesity [282] and hypertension [283] prevalence in those aged 18 years and over were available for birth cohorts 1921 to 1965 from the World Health Organisation (WHO). HSE midlife prevalence was plotted against prevalence from WHO and the correlation was used to estimate midlife prevalence for remaining birth cohorts.

HSE data [284] was extrapolated using linear trends for future smoking estimates then applied to CFAS II 2011 estimates as these differed between HSE and CFAS II. HSE data [284] was used for future stroke trends using linear extrapolation. Stroke estimates in 2011 were similar in CFAS II and HSE so HSE trends were not applied to CFAS II estimates.

6.3.4 Dementia Forecasts

The forecasts combine population estimates, current age and sex specific dementia prevalence, the relative risk between risk factors and dementia, the correlation between risk factors for dementia, and prevalence trends of dementia risk factors. Methods from Norton et al. [38] extended methods from Nepal et al. [268] to adjust for many risk factors. Steps for forecasting future dementia cases and dementia prevalence in five year intervals for those aged 65 years and above:

1. Population ageing (extrapolation model)
   This forecast assumed age and sex specific dementia prevalence remained the same, combining CFAS II 2011 estimates [7] with age and sex specific population forecasts from the ONS [8].
2. Population ageing and accounting for a single risk factor (single forecasts)
   Including a risk factor modifies the age and sex specific dementia prevalence over time. These forecasts model influence of the risk factor on dementia prevalence in five year intervals. Risk factors were either binary or categorical. Dementia prevalence in the risk

factor reference category (P_{gp_1}), category 1 here for ease, is given by the following equation that was derived by Nepal et al. [268]:

$$P_{gp_1} = \frac{P_{tot} \times N_{tot}}{N_{gp_1} + \left(RR_{gp_2} \times N_{gp_2}\right) + \cdots + \left(RR_{gp_i} \times N_{gp_i}\right)}, \quad (6.1)$$

where P_{tot} is age and sex specific dementia prevalence, N_{tot} is number of people in that age and sex group, i is number of categories in a risk factor, N_{gp_i} is number of people in age and sex specific category i of the risk factor and RR_{gp_i} is the relative risk associated with being in category i compared to the reference category ($i = 1$). To calculate age and sex specific dementia prevalence in other categories of the risk factor ($i \neq 1$), dementia prevalence in the reference category was multiplied by relative risk of being in category i:

$$P_{gp_i} = RR_{gp_i} \times P_{gp_1}. \quad (6.2)$$

This was repeated for each category of a risk factor in an age and sex specific group. To calculate age and sex specific dementia numbers in each category of the risk factor, dementia prevalence in the age, sex, risk category group was multiplied by number of people in the age, sex, risk category group. Summing together gave dementia cases in an age and sex group. The new dementia prevalence in an age and sex group is the total dementia number in that age and sex group divided by the total number of people in the population in that age and sex group. If risk factor prevalence changes over time then so will dementia prevalence. Age sex risk category specific dementia prevalence and relative risk were assumed constant over time. Example 1 in Appendix A3 gives an application of these methods.

3. Population ageing and accounting for multiple risk factors (combined forecasts)

To account for risk factor interaction Norton et al. [38] methods were used. Unadjusted PAF [238] was multiplied by a weight (w):

$$Weighted\ PAF = w \times \frac{P(RR-1)}{P(RR-1)+1}. \quad (6.3)$$

Where w was uniqueness (1 – communality [285]) found using principal component analysis on a correlation matrix of all the risk factors in 2006 HSE data (Table 6.1) [286]. After weighting, the weighted PAF, w and P were kept constant so that the formula could be rearranged to get an adjusted relative risk (RR_a – Table 6.1). Multiple risk factor dementia forecasts were built in layers. Dementia was forecasted adjusted for the first risk factor using adjusted relative risk (RR_a) instead of original relative risk in Equations 6.1 and 6.2. Adding risk factors uses the same method but to impose the difference the first risk factor makes, Equation 6.1 was adjusted such that P_{tot} (the prevalence of

dementia in an age and sex group) was from the dementia forecast using the first risk factor rather than the original prevalence of dementia from CFAS II. When calculated at other five year time points the original prevalence of the second risk factor was still used in Equation 6.1 so that changes to the prevalence of the second risk factor over time were taken into account. Again, relative risk was assumed constant over time. Example 2 in Appendix A3 gives the application of these methods.

4. Forecasting overall prevalence

   Dementia prevalence at each time point was dementia cases in each age and sex group summed divided by total population at the time point.

6.3.5 Risk reduction scenarios

On the basis of single forecasts, two modifiable risk factors were chosen to model scenarios for risk reduction. Public health interventions now could result in fewer dementia cases in the future. Reduction in prevalence of late life risk factors now could impact dementia prevalence by 2020 and reductions in midlife risk factors by 2030. The first scenario was a relative reduction to risk factor prevalence of 5% per year, and the second, a relative reduction of 10% per year.

6.4 Results

6.4.1 Risk factor trends

Table 6.1 summarises risk factor prevalence trends. Higher education increased over time (Figures 6.3 and 6.4). The marked change in 9 years or less and 10-11 years of education coincided with an increase in UK compulsory school leaving age. Obesity prevalence increased by both age and birth cohort between the ages 45-55 years, mainly for men (Figure 6.5) but also for women (Figure 6.6). Applying the correlation between HSE and WHO estimates (Figure 6.7), midlife obesity prevalence increased over time (Figure 6.8). Hypertension in men remained stable by age for ages 45-55 years but decreased by birth cohort (Figure 6.9). In women, hypertension increased with

age but decreased by birth cohort for ages 45-55 years (Figure 6.10). Applying the correlation between HSE and WHO estimates (Figure 6.11), midlife hypertension prevalence decreased over time (Figure 6.12). Current and past smoking decreased over time in men (Figure 6.13). In women current smoking decreased over time but past smoking remained stable (Figure 6.14). Applying these trends to CFAS II estimates for smoking gives the trends in Figures 6.15 and 6.16. Stroke prevalence increased over time, mainly in men aged 75 and over (Figure 6.17).

Figure 6.3: Education in men by birth cohort from CFAS for all birth cohorts up to 1941-1945 (vertical line). For birth cohorts not seen in CFAS, estimates for 9 years or less of education were assumed to remain the same as 1936 to 1945, 12 years or more education estimates were from GHS and 10 to 11 years of education was the remainder after these two were summed.

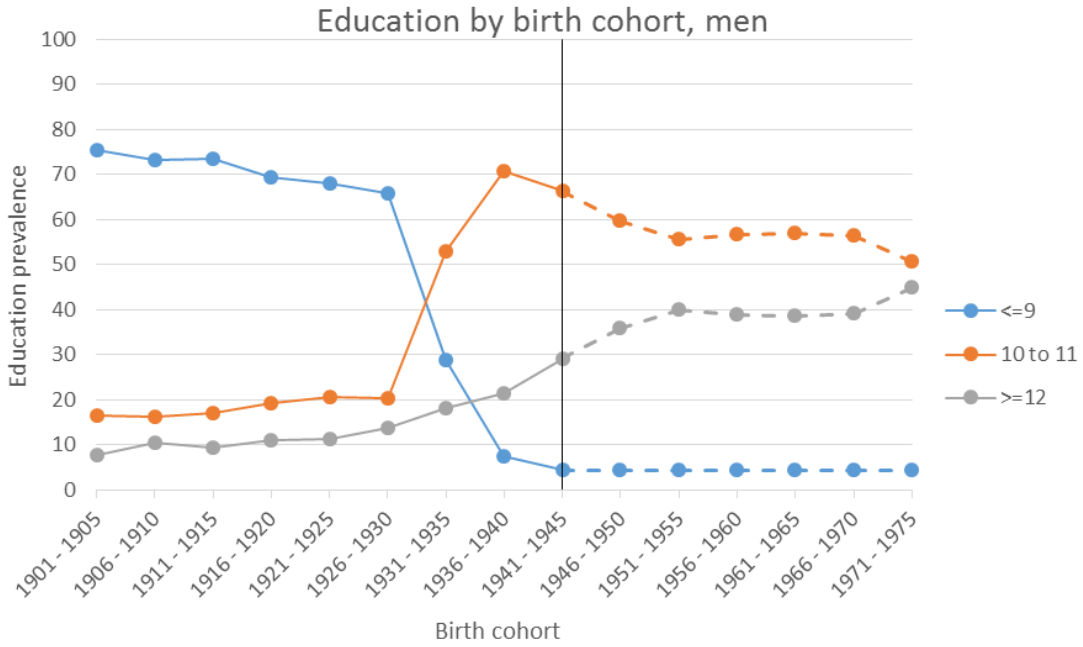


Figure 6.4: Education in women by birth cohort from CFAS for all birth cohorts up to 1941-1945 (vertical line). For birth cohorts not seen in CFAS, estimates for 9 years or less of education were assumed to remain the same as 1936 to 1945, 12 years or more education estimates were from GHS and 10 to 11 years of education was the remainder after these two were summed.

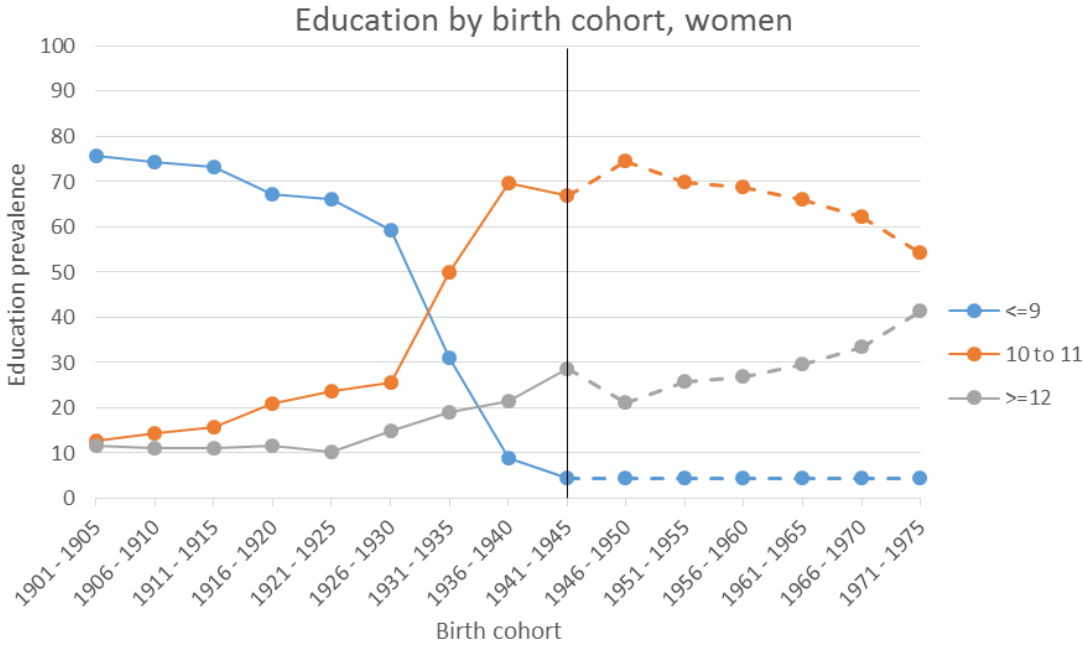


Figure 6.5: Obesity prevalence for men by age in all birth cohorts that included any age in the age range 45-55 years from the Health Survey for England time series data. o Δ are estimates based on less than 150 observations.

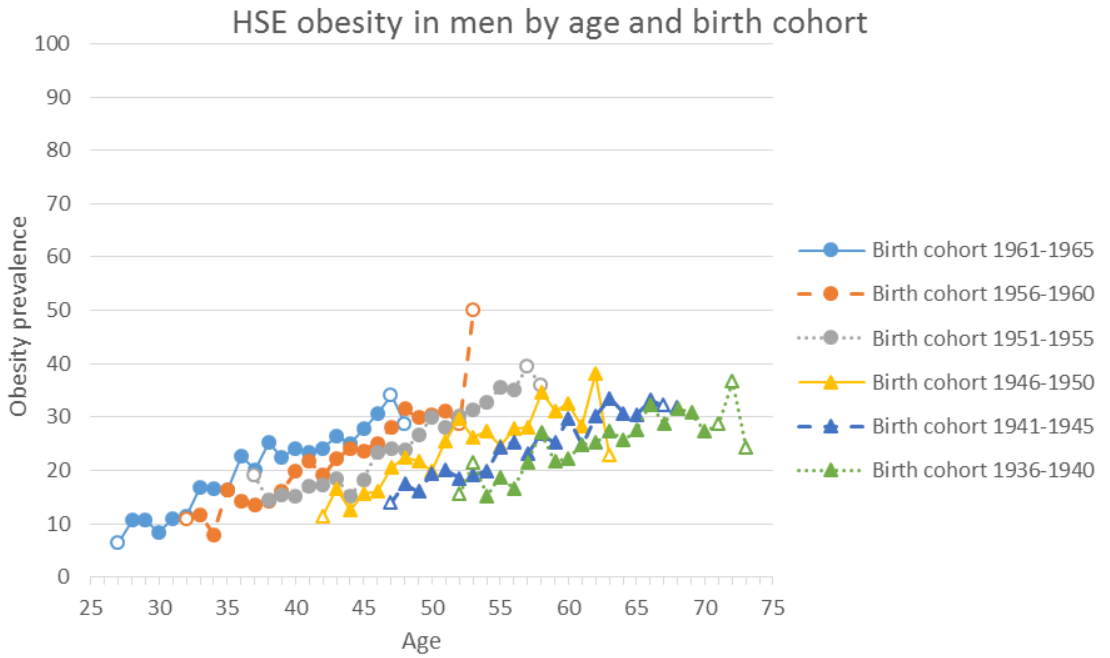


Figure 6.6: Obesity prevalence for women by age in all birth cohorts that included any age in the age range 45-55 years from the Health Survey for England time series data. o Δ are estimates based on less than 150 observations.

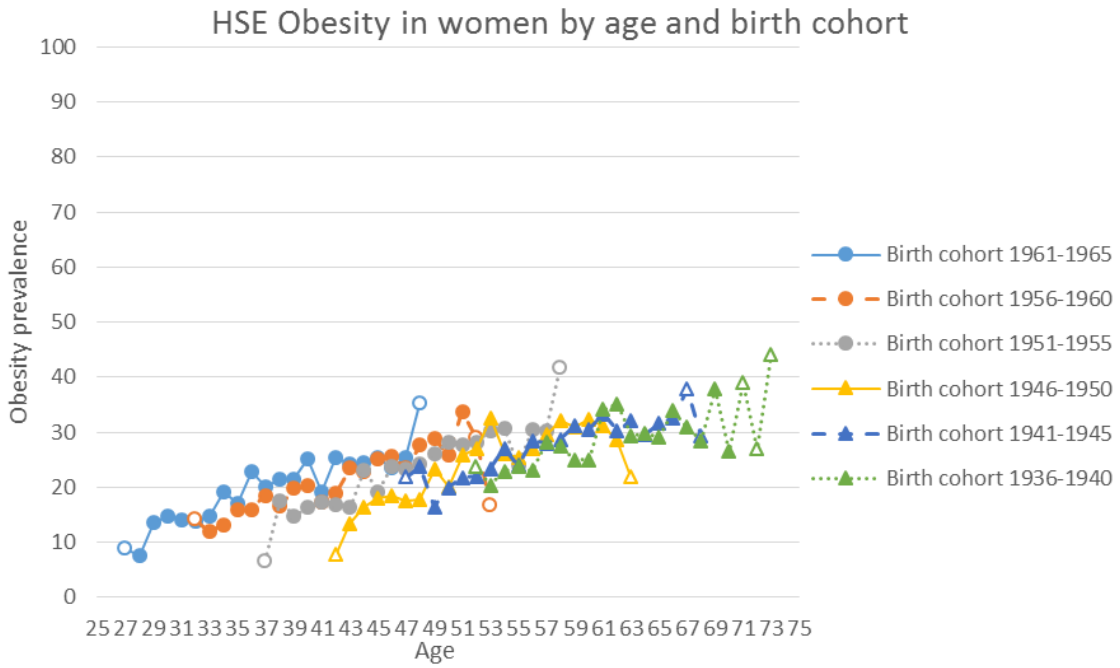


Figure 6.7: Relationship between prevalence seen in WHO UK population obesity prevalence estimates in those aged 18 or over in comparison to those aged 45-55 in HSE for matching birth cohorts

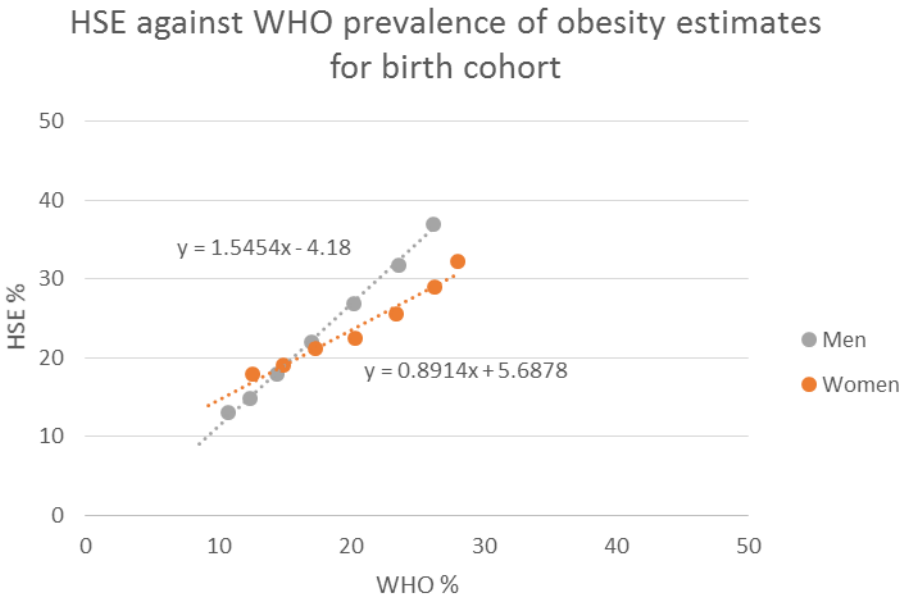


Figure 6.8: Midlife obesity trends by birth cohort from HSE. Birth cohorts not covered by HSE (dashed plots before vertical line) estimates were extended by using WHO estimates using the relationship between HSE and WHO prevalence (Figure 6.7).

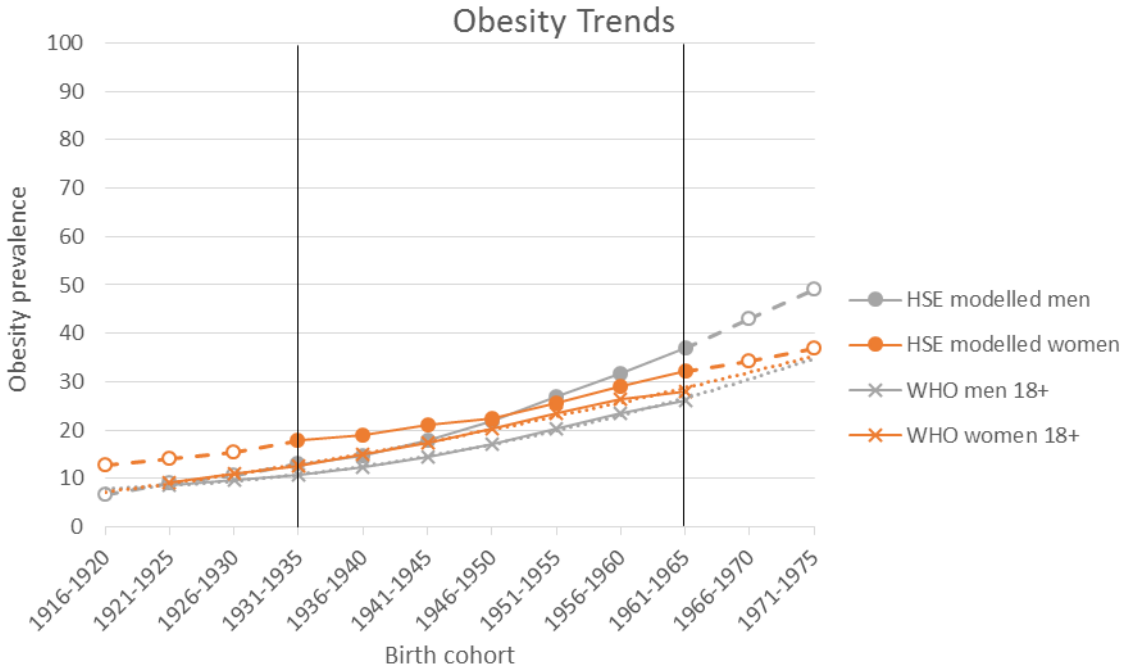


Figure 6.9: Hypertension prevalence for men by age in all birth cohorts that included any age in the age range 45-55 years from the Health Survey for England time series data. o Δ are estimates based on less than 150 observations.

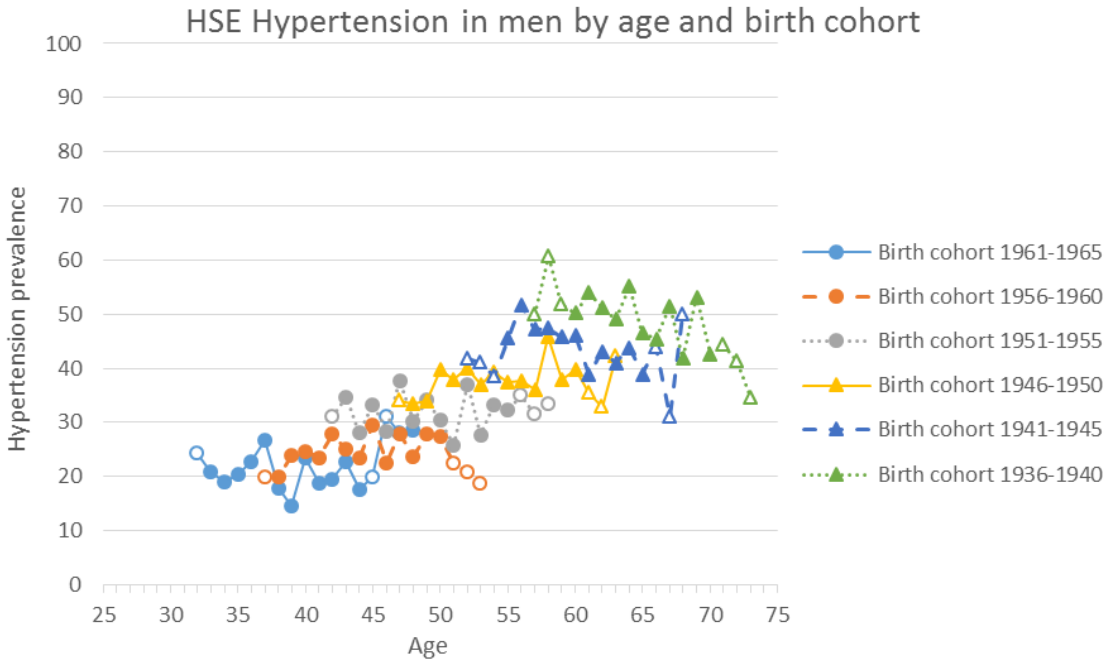


Figure 6.10: Hypertension prevalence for women by age in all birth cohorts that included any age in the age range 45-55 years from the Health Survey for England time series data. o Δ are estimates based on less than 150 observations.

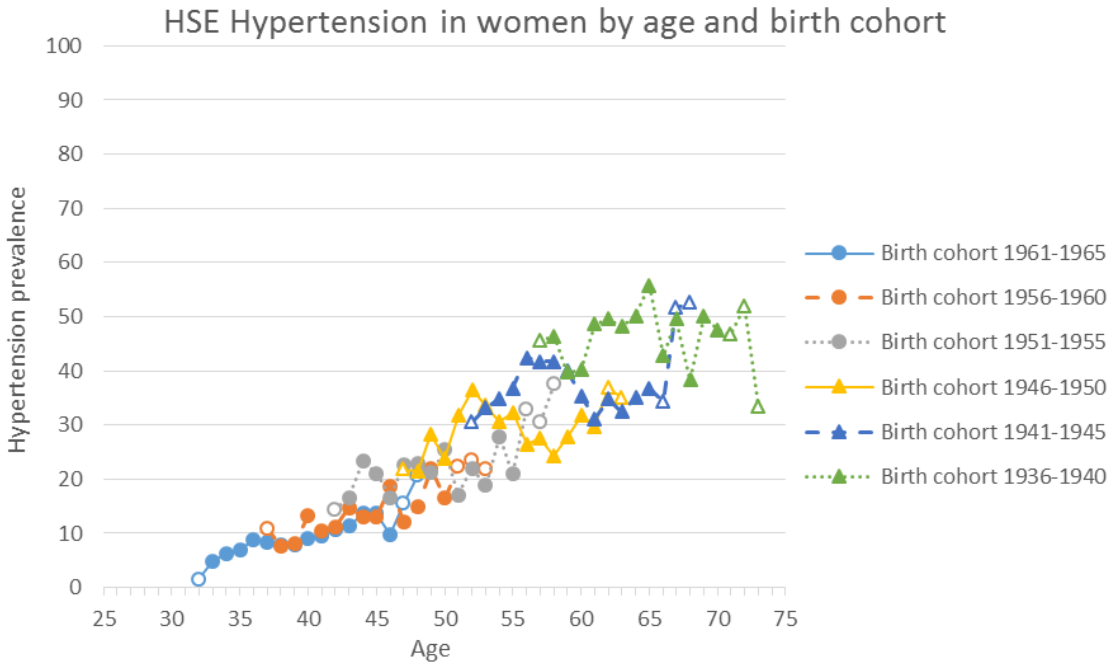


Figure 6.11: Relationship between prevalence seen in WHO UK population hypertension prevalence estimates in those aged 18 or over in comparison to those aged 45-55 in HSE for matching birth cohorts.

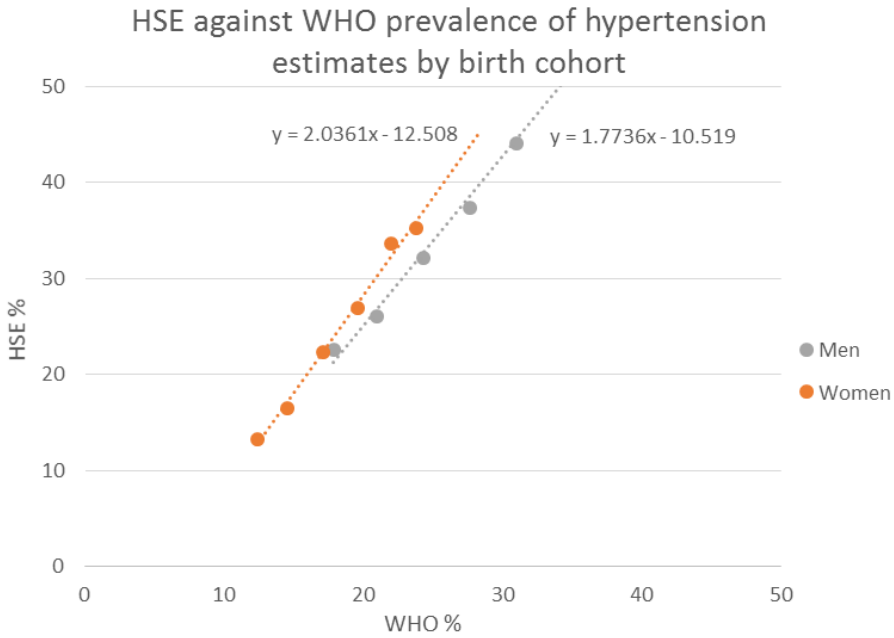


Figure 6.12: Midlife hypertension trends by birth cohort from HSE and ONS. For birth cohorts not covered by HSE estimates (Dashed plots before vertical line) were extended back using the relationship between HSE and WHO prevalence (Figure 6.11).

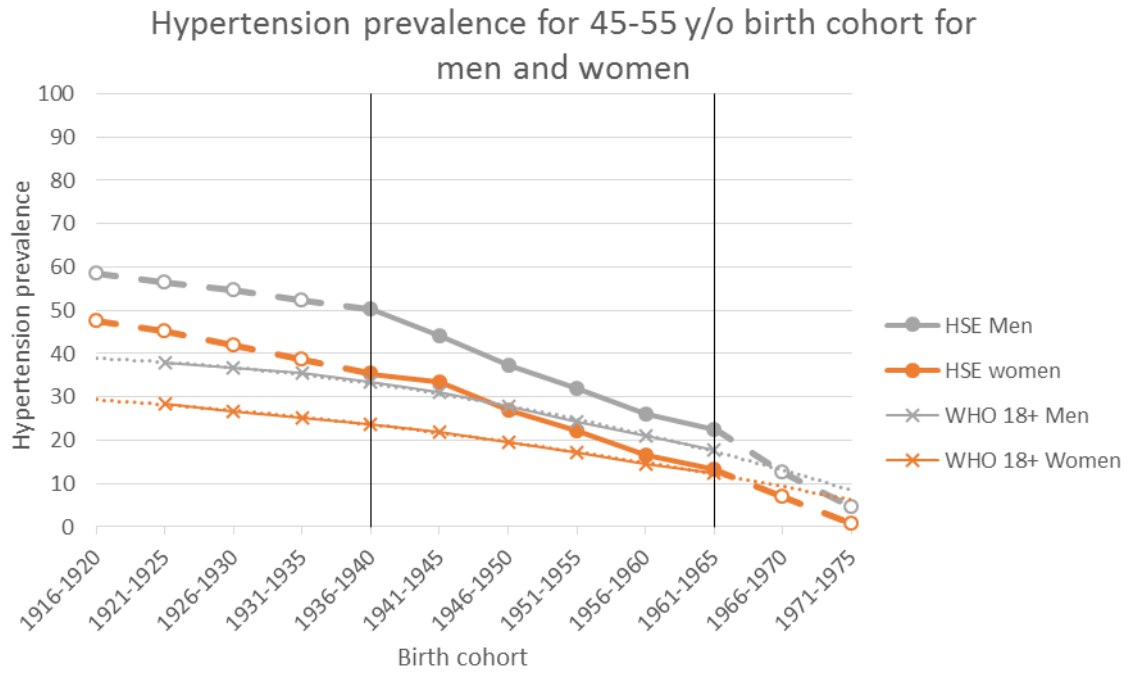


Figure 6.13: Smoking prevalence trends until 2040 by status of smoking in men from HSE trend data.

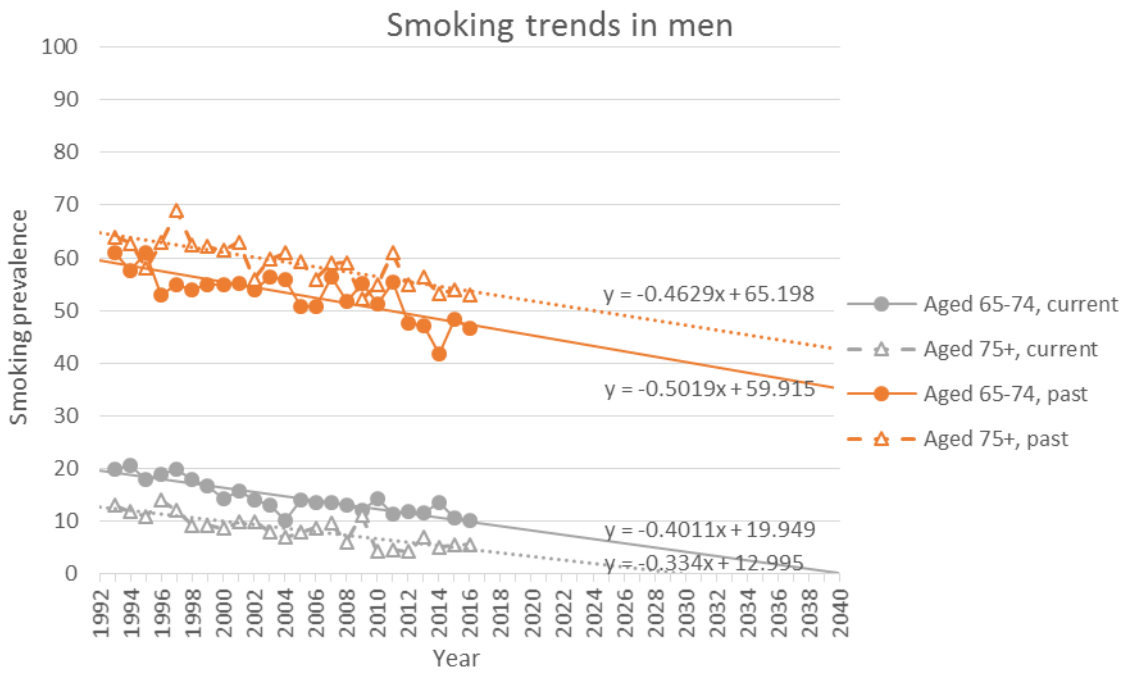


Figure 6.14: Smoking prevalence trends until 2040 by status of smoking in women from HSE trend data.

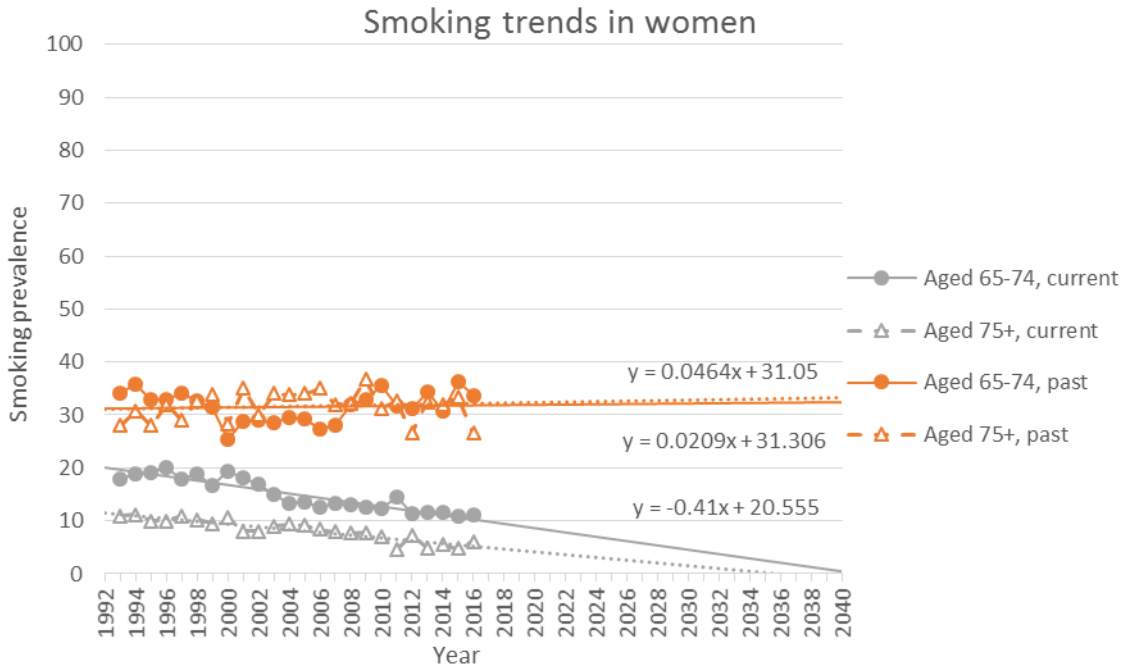


Figure 6.15: Smoking prevalence trends in men for 2011 onwards using CFAS estimates for 2011 and trends from HSE.

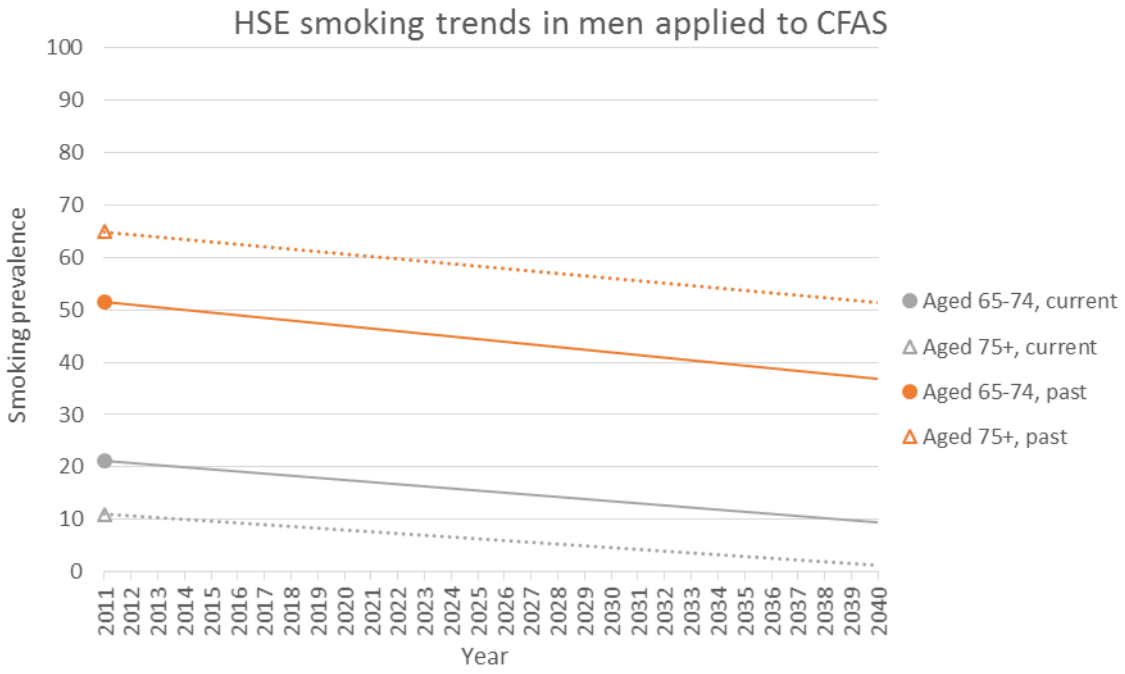


Figure 6.16: Smoking prevalence trends in women for 2011 onwards using CFAS estimates for 2011 and trends from HSE.

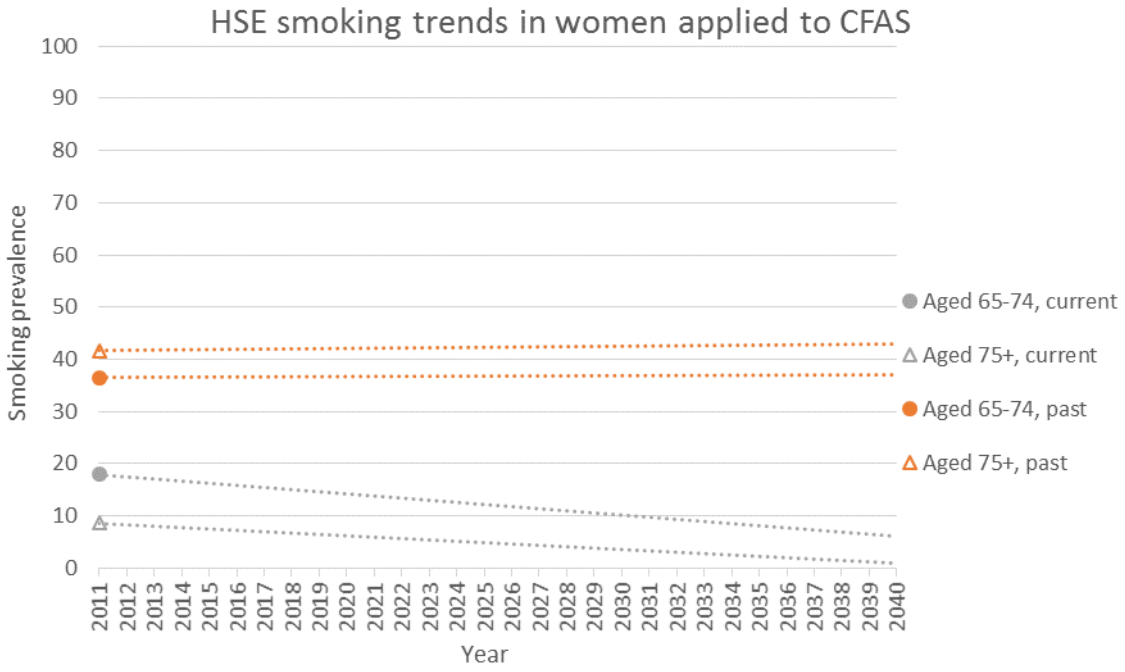
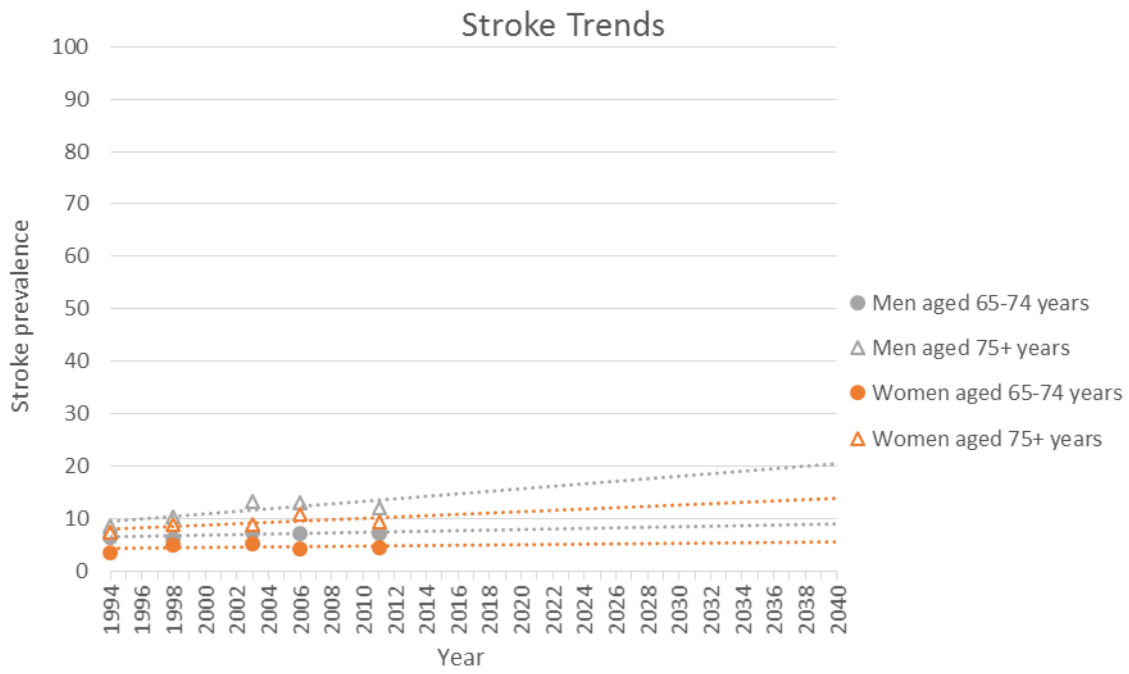


Figure 6.17: Stroke prevalence trends over years in men and women aged 65-74 and 75+ from HSE trend data.



6.4.2 Forecasts

An estimated 675,695 people in the UK met dementia criteria in 2011. Accounting only for population ageing, this increased to 1,325,107 in 2040, resulting in overall prevalence increasing to 7.5% (Table 6.2). Figure 6.18 gives the population ageing forecast and forecasts accounting for population ageing and one risk factor. The single risk factor forecasts show the extent to which risk factor changes could impact future dementia. Current midlife obesity trends could increase dementia cases to 1,446,197 in 2040 whilst stroke trends could increase dementia cases to 1,354,158 in 2040. Education as a protective factor only increased dementia cases to 1,109,215 in 2040 with dementia prevalence potentially decreasing over time (Table 6.2). Smoking and midlife hypertension prevalence decreased sufficiently to offset their association with increased dementia risk (Figure 6.18). Not enough, however, to prevent an increase in dementia prevalence (Table 6.2).

Table 6.2: Forecasted dementia prevalence estimates for those aged 65 years and over in the UK up to 2040

	2011 (%)	2020 (%)	2030 (%)	2040 (%)
Population ageing only	6.5	6.4	6.7	7.5
Population ageing and midlife obesity	6.5	6.5	7.1	8.2
Population ageing and education	6.5	5.8	5.7	6.3
Population ageing and smoking	6.5	6.3	6.6	7.2
Population ageing and midlife hypertension	6.5	6.3	6.5	6.9
Population ageing and stroke	6.5	6.4	6.8	7.6
Population ageing, midlife obesity and education	6.5	6.2	6.5	7.3
Population ageing, midlife obesity, education, smoking, midlife hypertension and stroke	6.5	6.2	6.4	7.1

Figure 6.19 gives the combined forecasts. Increases in compulsory education could outweigh detrimental influences from increasing midlife obesity prevalence. Comparing the fully combined forecast to the population ageing only forecast (extrapolation forecast) shows how much of a difference accounting for risk factor trends could impact expected dementia cases. In comparison to the extrapolation forecast accounting for these five risk factors greatly attenuates expected dementia cases in the future with 1,262,442 expected dementia cases in 2040 (prevalence 7.1% – Table 6.2), in comparison to 1,325,107 from the extrapolation forecast (prevalence 7.5% – Table 6.2).

Figure 6.18: Forecasting people with dementia in those aged 65 years and over in the UK up to 2040. First taking into account population ageing, then in addition a single risk factor.

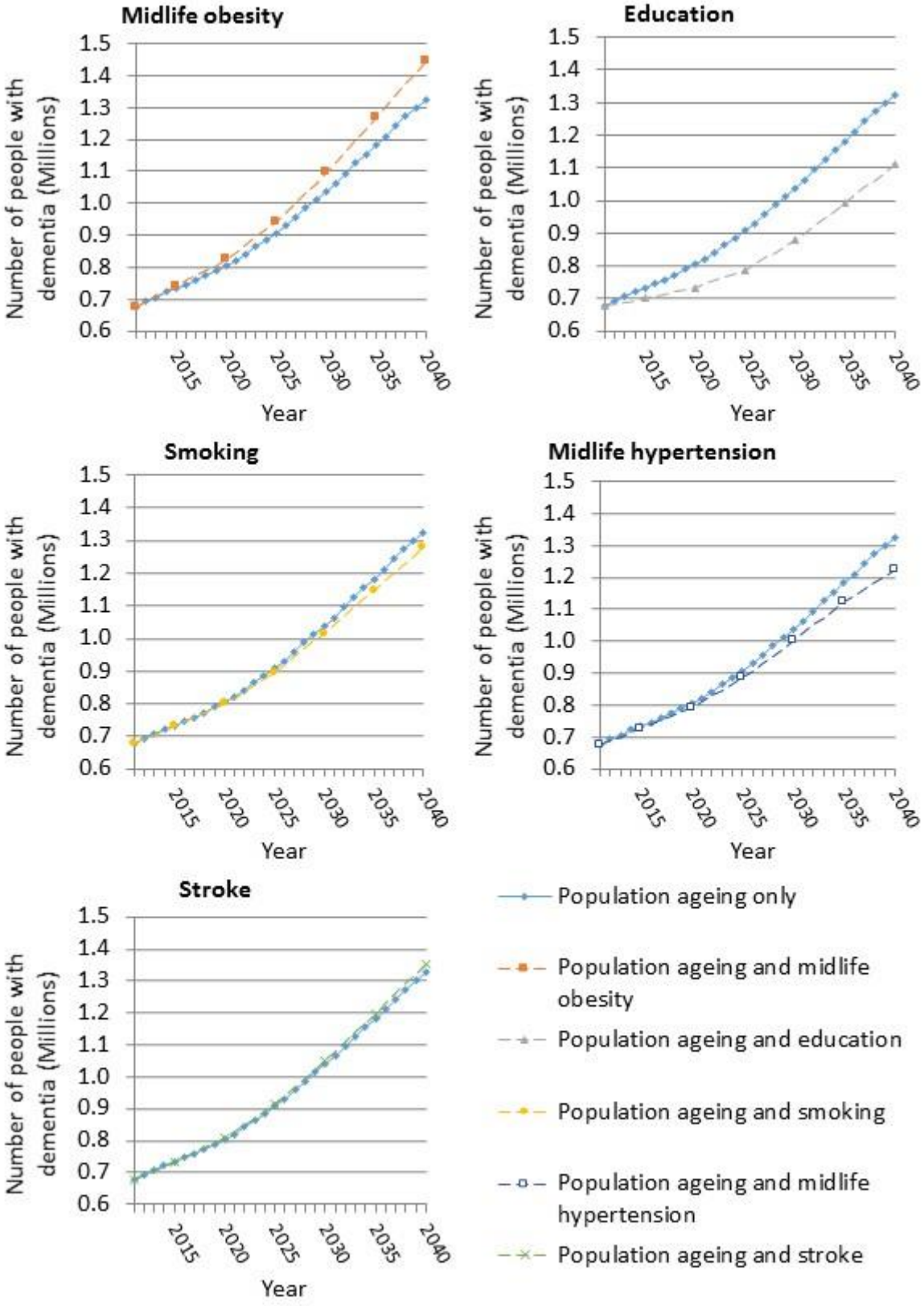


Figure 6.19: Forecasting number of people with dementia in those aged 65 years and over in the UK population to 2040. First taking into account only population ageing then taking into account obesity only (as in Figure 6.18 but here for comparison) and then combining with education and all risk factors considered in this analysis.

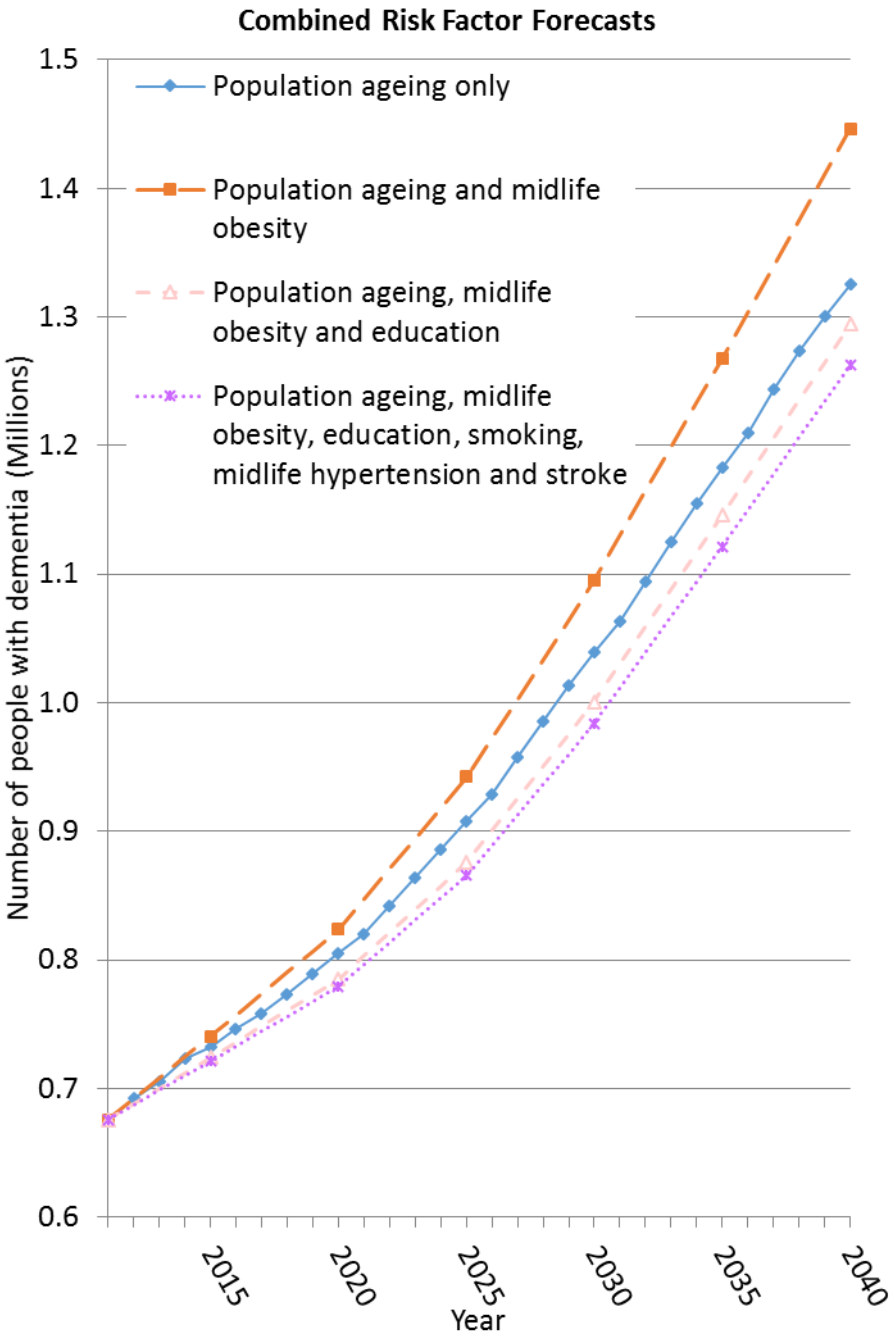


Table 6.3 gives risk factor reduction results. Stroke scenarios do not diverge from current trends until 2020, and midlife obesity scenarios until 2030. A 5% relative reduction in stroke prevalence per year from 2020 reduced expected dementia cases in 2040 from 1,262,442 to 1,232,521. A 10% relative reduction in stroke prevalence reduced dementia cases in 2040 to 1,225,429. A 5% relative reduction in midlife obesity prevalence per year from 2030 could reduce estimated dementia cases from 1,262,442 to 1,207,339 in 2040. A 10% relative reduction in midlife obesity prevalence reduced estimated dementia cases to 1,187,542 in 2040.

Table 6.3: Estimated number of people with dementia in 2020, 2030 and 2040 under the current risk factor trends and looking at scenarios of reduction for risk factors with either a 5% or 10% reduction in prevalence per year of stroke or midlife obesity.

		2020	2030	2040
All risk factors	Current trend	779,289	1,121,223	1,262,442
Stroke	5% reduction	779,289	971,762	1,232,521
	10% reduction	779,289	965,970	1,225,429
Midlife Obesity	5% reduction	779,289	983,891	1,207,339
	10% reduction	779,289	983,891	1,187,542

6.5 Discussion

As seen in previous chapters, education plays a large role as a protective factor, potentially reducing future expected numbers of people with dementia. When combining all five risk factors considered here both number of people with dementia and prevalence of dementia increased from now until 2040. The fully combined forecast also shows the extent to which dementia forecasts taking into account risk factor trends could differ from extrapolation forecasts. Prevention of stroke and midlife obesity have the potential to reduce expected future number of dementia cases.

6.5.1 Strengths and limitations

Dementia cases and prevalence were forecasted accounting for population ageing, risk associated with dementia, dependence between risk factors and trends in risk factor prevalence. This was the first dementia forecast for the UK that took into account trends in risk factor prevalence over time. In addition, large amounts of longitudinal data were not needed for the forecasts.

The largest limitation was that mortality was not included in these models. Mortality risk increases for those with dementia in comparison to those without dementia [287] and this is also true for midlife obesity [288, 289], stroke [290, 291], midlife hypertension [292] and smoking [293]. Mortality is lower in higher educated groups [294]. Any differences in life expectancy for risk factors will also indirectly impact mortality in people with dementia as well. Risk of mortality for different health conditions has also changed over time with advances in medicine and care, for instance, mortality risk from stroke has declined over time [295]. Mortality has been included in forecasting models in two ways previously, by using multistate illness-death models (as in macro and micro-simulation models) or by weighting for risk of mortality from a risk factor [267]. Multistate modelling needs an extensive amount of longitudinal data not available at the time of this analysis in CFAS II. Although CFAS I had longitudinal data, mortality has changed to such an extent in the last two decades that the representativeness would be limited. Recently, to overcome this issue in CFAS II, other datasets (Understanding Society and ELSA) have been included at baseline to allow micro-simulation. Combining datasets involves a lengthy setup period. Given micro-simulation is already time consuming, this method was developed as a faster but maybe less accurate way of forecasting dementia whilst still including dementia risk, dementia risk factor prevalence trends and changes to demographics over time in the forecasts. To weight for mortality a dataset with all the risk factors, dementia and death would be needed to allow adjustment for the overlap between risk factors and dementia. Neither CFAS I or CFAS II included all the risk factors. Even when weighting for differences in mortality from dementia risk factors, differences in mortality risk from dementia would not be included or changes in mortality over time. It is difficult to tell how mortality would impact the models. In the model currently the declining prevalence of midlife hypertension and smoking compensates for the increase in risk of dementia. When incorporating mortality into the model, intuitively there will be less people at risk of dementia and therefore there could be less people developing dementia in the future. However, life expectancy will be higher for those without midlife hypertension and for those who

do not smoke and age is one of the greatest risk factors for dementia (Chapter 4), therefore when incorporating mortality in the model, declining prevalence of these two risk factors could result in more people developing dementia.

The accuracy of these forecasts is probably between that of extrapolation and single factor forecasts and that of macro- and micro-simulation models as they are able to take into account multiple risk factor trends but not able to take into account mortality. However, another limitation to these forecasting models was that confidence intervals could not be estimated as error estimates for all components of the forecasts were not available. Therefore these results should be interpreted with caution as accuracy of the estimates is unknown. An assumption of causality was made between the risk factors and dementia and relative risk was assumed constant over time. Evidence from other studies [23, 49] and from Chapter 4 suggests some risk associations have changed over time but different risk factors were highlighted in each analysis. If future research confirms these results, relative risk changes could be incorporated into the models by changing estimates for relative risk at different time points. As CFAS I and CFAS II participants were aged 65 years and over, no midlife risk of dementia could be measured. Applying risk world literature to a single country has limited generalizability because of differences in treatment and care, study design or methodology, or genuine differences over time. Meta-analysis was used to combine evidence and give estimates for risk of dementia from midlife obesity and midlife hypertension.

Hypertension prevalence and risk in this model was for measured blood pressure, whether or not someone was taking anti-hypertensive medication. If prevalence for medicated hypertension and measured blood pressure was available this would be preferable as it is possible that hypertension exhibits detrimental effects on the brain before being treated. Evidence from Chapter 4 suggests that prevalence of hypertension is increasing over time but this is for later life hypertension rather than midlife hypertension. As the self-reported data includes treated and untreated hypertension it is not surprising that the trend is opposite to hypertension measured only using blood pressure measurement. As the use of anti-hypertensive drugs has increased at a fast rate in recent years when hypertension prevalence was extended backwards the prevalence was high for the 1916-1920 birth cohort. However, as the prevalence was very similar to current levels of late life hypertension, this was used in the absence of any better alternative. Also, as this

was only for one birth cohort that contributes to only one age group at a given time point for the forecasts it should have minimal impact.

6.5.2 Interpretation of results

These forecasts estimated that 7.1% or 1,262,442 people aged 65 years and over would have dementia in 2040 in the UK. The fully combined model shows how important it is to take risk factor trends into account when forecasting dementia. As expected, these results were more conservative in comparison to the published extrapolation model estimating 1,750,000 people with dementia by 2040 [2]. Both macro-simulation models of dementia for the UK predicted different numbers of people with dementia in 2040, one estimating 1,730,000 people with dementia in 2040 [38] and the other estimating 1,204,500 dementia cases in 2040 [150]. The results from this analysis were at the lower end of this range for number of people with dementia in the UK in 2040. The micro-simulation model predicted 8.5% or 1,227,500 people with dementia in 2035 in comparison to 6.7% or 1,121,223 people with dementia estimated here. This will be discussed later.

Given the extent to which results changed when accounting for these five risk factors in comparison to the extrapolation model, future research should aim to include as many risk factors for dementia as possible in forecasts. Each of the single risk factor forecasts exemplifies the magnitude to which an individual risk factor could alter dementia forecasts. The single risk factor forecast taking into account education trends was the only scenario that predicted dementia prevalence could continue to decline in the future as it has done in the last two decades [7]. Although in the fully combined model number of dementia cases and dementia prevalence increased in the future, it is unknown whether this would be the case if other risk and protective factors were considered. For instance if prevalence of other protective factors have been increasing over time this could outweigh increases in prevalence of risk factors resulting in an overall decrease in dementia prevalence in the future.

In comparison to UK forecasts estimating reductions in numbers of people with dementia due to prevention of risk factors [38] the results here for midlife obesity and stroke were conservative.

This could be because the reductions here were compared to the forecast that accounted for current risk factor trends, whereas previously reductions were compared to a macro-simulation model accounting for mortality. The results here and from Norton et al. [38] differ greatly to results from Ahmadi-Abhari et al. [150]. Sensitivity analysis was conducted to compare stable cardiovascular disease incidence to decreasing incidence of cardiovascular diseases. When cardiovascular disease incidence was stable the expected number of people with dementia in 2040 was reduced in comparison to decreasing incidence of cardiovascular diseases. This suggests the opposite to results here and from Norton et al. [38], that preventing risk factors for dementia will increase expected number of dementia cases in the future when accounting for mortality differences. The Ahmadi-Abhari et al. forecasts did not take into account current risk factor trends but a micro-simulation model that adjusts for mortality, risk associated with dementia and prevalence trends of risk factors over time agreed with the Ahmadi-Abhari et al. results [263]. That prevention of risk factors or curing risk factors will lead to an increase in risk of dementia and in years lived with dementia as the increases to life expectancy outweigh the benefits of being at lower risk of dementia [263]. This data is for the USA where current risk factor trends are different to in the UK, however, these results suggest that dementia risk and years living with dementia are expected to increase if some risk factors for dementia are eliminated, due to increases in life expectancy.

Results for risk reduction scenarios could provide insight into the difference in results here compared to the micro-simulation model of dementia for the UK [4]. This chapter has shown that prevalence of some protective factors (higher education) have already been increasing over time and prevalence of some risk factors (smoking and midlife hypertension) have already been decreasing over time. As these trends have already occurred (rather than hypothesized future reductions) then the estimates of dementia for 2035 from the micro-simulation model could be higher than results here for the same reason as future scenarios of risk reduction increase future dementia in comparison to baseline assumptions – increases in life expectancy from the current trends outweigh the benefits of being at decreased risk of dementia. Micro-simulation forecasts with risk reduction scenarios for the UK are crucial when considering prevention strategies for the future.

UK forecasts of other measures associated with dementia such as service use and care [296], cost [25], burden [29], disability [297] and multi-morbidity [4] will depend on the accuracy of dementia forecasts. Disability Adjusted Life Years (DALYs) are a measure of the number of years of life lost and have been used to estimate burden of dementia. DALYs due to dementia are expected to increase in the future as dementia increases [29]. Projections of care [25, 269, 296] and cost associated with care for people with dementia (even under a low expenditure scenario) [25] also increase in the future. Projections of cost took into account demand for long term care and care staff pay [25]. Disability associated with dementia will increase over time, predominantly in those aged 85 years or over [297]. When considering declining dementia incidence rather than stable dementia incidence over time, this was still the case [297]. Multi-morbidity overall is expected to increase in the future and the contribution of mental ill-health (including dementia, depression and cognitive impairment, no dementia) increases as a co-existing health condition [4].

6.5.4 Conclusions

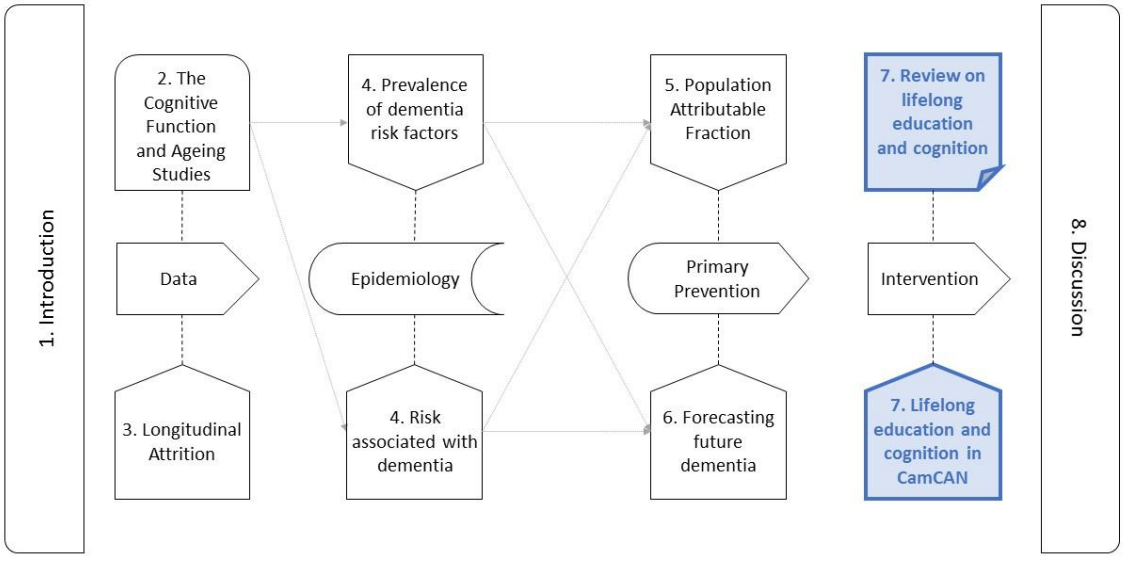
The fully combined model considered here shows that after taking into account current risk factor trends the outlook for dementia in the future may not be as bleak as suggested by just looking at trends in age and demographics (extrapolation model forecasts). Trends in protective factors such as education and prevention of risk factors could further reduce expected future cases. However, as these forecasts do not account for mortality the results should be treated with caution as forecasts accounting for mortality suggest decreasing risk factors for dementia will increase dementia and years living with dementia in the future. Micro-simulation models of future dementia in the UK looking at risk factor reduction are essential to accurately predict the impact of preventative strategies.

Chapter 7: Lifelong education and dementia

7.1 Chapter overview

Education has continuously been highlighted as a protective factor against dementia. Whilst many individuals complete their education in young adulthood, some continue to study into mid- and later-life. If lifelong education is a protective factor against dementia this could have vast implications for intervention initiatives for tackling dementia.

The purpose of this chapter was to assess whether midlife or later life education is associated with dementia independently of young adulthood education through a systematic review and analysis of a population based cohort.



7.2 Background

Chapters 4, 5 and 6 showed that education was promising as a protective factor of dementia with potential to influence population levels of dementia. In previous chapters, only young adulthood education was considered rather than over the life course. As discussed in Chapter 1, the mechanism behind the protective association between education and dementia has been described as due to the emerging concept of cognitive reserve [73, 298-300]. Occupation and cognitive leisure activities are also thought to contribute to cognitive reserve. Having high cognitive reserve is thought to increase the efficiency of existing neural networks thereby preserving cognitive function and delaying the clinical manifestation of dementia, despite the presence of neurodegenerative pathology. The concept of cognitive reserve (also known as cognitive lifestyle [74, 301] or brain reserve [196, 302], although slightly varying definitions are being proposed for these terms) has been developed out of an extension of the work around the impact of education on the brain [299, 301]. High cognitive reserve is associated with decreased dementia risk and has been shown to attenuate the rate of cognitive decline [74, 303]. There is also some evidence that high cognitive reserve could help reverse cognitive decline from slight cognitive impairment back to normal cognition [97], however it is not clear whether poor cognitive engagement is a cause or effect of early cognitive change [304]. In a review of reviews Harrison highlighted the need for further work in this area, given its potential impact on delaying the onset and progression of dementia [305].

There is a common misconception that the advantages of higher education continue into being employed in more highly skilled occupations. However, Chapter 4 presented evidence to the contrary of the common notion that higher education results in more skilful employment. Further analysis of CFAS I and CFAS II showed that although overall occupation levels remained stable over time, this was not true within each education group with a large decrease in the proportion of those with 10-11 years of education reporting highly skilled occupations (Figure 4.1). If higher education is unlikely to advance career prospects individuals may benefit less from increasing cognitive reserve in mid- and later-life. Whilst previous research has predominantly been focused on education in early life, education is increasingly being suggested as a potential modifiable factor later in life [40, 44].

Given the above there has recently been an increase in trials studying the effect of interventions that target multiple leisure activities as part of cognitive reserve with varying success [306]. These include: the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment (FINGER - [307]), a Multidomain Approach for Preventing Alzheimer's Disease (MAPT - [308]), Prevention of Dementia by Intensive Vascular Care (PreDIVA - [309]), Healthy Ageing Through Internet Counselling in the Elderly (HATICE - [310]), and the Innovative Midlife Intervention for Dementia Deterrence (In-MINDD - [311]). Results have been published from PreDIVA [312], MAPT [313] and FINGER [314]. The interventions considered by these three trials varied in intensity but all coveres three broadly similar areas; cognitive and social activities, nutrition and physical. The intervention was most intense in FINGER, the only trial to find improved cognition amongst those in the intervention group compared to the control group [314].

The purpose of this chapter is to assess whether education could potentially be utilised in the same way as other areas of cognitive reserve – as an intervention for dementia. First, results from current literature on the subject need to be summarised through systematic review.

7.3 Systematic review on lifelong education and dementia

In order to evaluate current literature on the topic of lifelong education and dementia a systematic review was conducted. A search of Scopus on 22nd May 2018 using the search terms (((educat* OR learn* OR train*) W/4 (lifelong OR "life long" OR lifecourse OR "life course" OR adult OR midlife OR "mid life" OR "middle age" OR "late* life" OR lifetime OR "life time" OR lifespan OR "life span")) OR "universit* of the third age") AND (dement* OR Alzheimer*) in the title and abstract returned 561 results after exclusion of duplicates. There were a few inclusion criteria to select publications:

- Education after young adulthood had to be reported
- Education after young adulthood did not include other cognitive reserve measures or cognitive training
- The outcome had to be dementia or Alzheimer's disease, not cognition
- Findings had to be contemporary, not a review.

After the title and abstract screen 28 papers remained, the predominant reason for exclusion was that education was confined to young adulthood. There were no remaining results after full text screen. The most relevant studies used cognition as the main outcome measure in participants who already had dementia, dementia was therefore not the outcome [315, 316].

7.4 Systematic review on lifelong education and cognition

Due to the lack of evidence with dementia, the decision was made to expand the review into the impact of lifelong education on cognition.

7.4.1 Methods

A systematic review of the literature was conducted in the Scopus database. A single reviewer and database was searched. The search strategy included variations on the phrase “lifelong education” and dementia, Alzheimer’s disease and cognition (see below). The search was conducted on 19 June 2018 and all literature published up to this date were eligible for inclusion.

The complete search string for Scopus was:

(((TITLE-ABS-KEY (educat* OR learn* OR train*)) W/4 (TITLE-ABS-KEY (lifelong OR "life long" OR lifecourse OR "life course" OR adult OR midlife OR "mid life" OR "middle age" OR "late* life" OR lifetime OR "life time" OR lifespan OR "life span"))) OR (TITLE-ABS-KEY ("universit* of the third age"))) AND (TITLE-ABS-KEY (dement* OR alzheimer* OR cognit*))

Where * is the wildcard operator that includes all permutations of the word in the search. Variations on the same phrase were linked together using the operator OR and for the search to also include dementia, Alzheimer’s disease and cognition terms the AND operator was used. The operator W/4 indicates that the variations for “lifelong” have to be within four words of the variations for “education”. This was used to pick up lifelong education and cognition rather than education and lifelong cognition.

Any original peer-reviewed articles on lifelong education and cognition were included. Given that there is no established way of measuring education later in life any formal courses were included in the definition. Articles on cognitive training and cognitive reserve were excluded, as were any studies that only included education in young adulthood and nothing on education later in life. Reviews and non-human studies were also excluded.

A title and then abstract screening were administered to all search results, selecting articles for full-text screening. There were no language restrictions and any non-English articles were first translated through Google. Any data on average cognition in separate educational groups, or associations between lifelong education and dementia were extracted.

7.4.2 Results

After duplicates were excluded there were 4,332 articles for title screening. Figure 7.1 shows each stage of the exclusion process. Title screening left 274 remaining articles for abstract screening, of which 74 went through to full-text screening. Most of these articles were ineligible for the review (n=71), out of those that were ineligible the main reason was because education had not been measured at different life stages (n=51). Some studies included lifelong education and a measure of cognition but not a group without education later in life for comparison [315-318]. This resulted in three studies being included in the review [319-321]. References of these three studies were searched and of 17 potential references to be included, 5 went through full text review and 1 more study [322] was included in the review, making a total of four studies in the review.

Figure 7.1: Flow through literature review

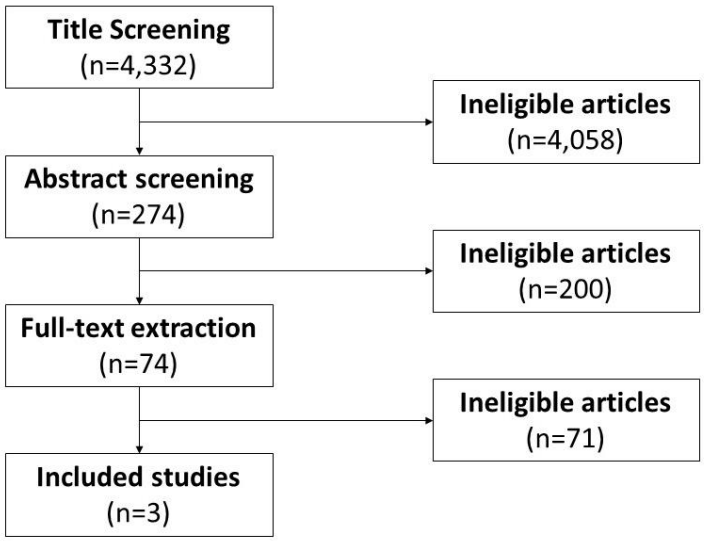


Table 7.1: Details of studies included in the review

Article	Lifelong education measure	Cognition measure	Details
Fernández-Ballesteros et al. 2012 [321]	Three years of university level education in later life	Digit-Symbol Test from the Wechsler Adult Intelligence Scale	Quasi-experimental group were 56 individuals from the University Program for Older Adults in Spain Quasi-control group were 39 volunteers from the Longitudinal Study of Active Ageing. Repeated measures ANOVA and ANCOVA used for analysing differences between groups.

Article	Lifelong education measure	Cognition measure	Details
Hatch et al. 2007 [319]	Any formal courses grouped into: no adult education, some education but with no resulting qualifications, some education with a resulting qualification up to O level or equivalent, some education with a resulting qualification of at least A level or equivalent	Previous cognitive ability measured by tests devised by the UK National Foundation for Educational Research and the Watts-Vernon Reading Test. Cognitive outcomes at midlife measured by National Adult Reading Test, a 15-item word-learning task for verbal memory, verbal fluency measured by animal naming task, speed and concentration measured by a timed letter search	Subsample of 1,934 individuals from the British 1946 birth cohort. Analysis conducted using ordinary least squares regression with sensitivity analysis for missing data conducted using full information maximum likelihood regression.
Lenehan et al. 2016 [322]	Intervention group undertook at least one year of university study	Short Form 1 of the Wechsler Adult Intelligence Scale and the spelling and maths components of the Wide Range Achievement Test	Subsample of 459 participants from the Tasmanian Healthy Brain Project. Analysis conducted using Growth Mixture Modelling to identify unobserved subgroups based on cognition trajectories.
Thow et al. 2018 [320]	Intervention group undertook at least one year of university study	Separate neuropsychological tests for episodic memory, working memory, executive function and language processing control	Subsample of 444 participants from the Tasmanian Healthy Brain Project. Multiple group latent growth curve modelling used to model cognition trajectories in the intervention and control groups.

Table 7.1 gives a summary of studies included in the review. Meta-analysis was not considered as the studies varied greatly in design. Fernández-Ballesteros et al. [321] used a quasi-experimental case control design. Hatch et al. [319] analysed a longitudinal birth cohort study that followed

individuals from infancy. Both Lenehan et al. [322] and Thow et al. [320] used data from the Tasmanian Healthy Brain project (THBP), an intervention study on university education in later life where the voluntary intervention group completes at least one year of university level education. Three out of four of the studies only measured university level education, either as three years of full time university [321] or at least one year of full or part time university level education [320, 322]. Hatch et al. was the only study to look at education other than university level [319].

Cognitive measurement also differed between studies (Table 7.2). There were four broad cognitive domains covered, including episodic memory, working memory, executive function and language processing. Episodic memory is memory of specific events, working memory allows information to be held temporarily whilst being processed, executive function controls behaviours such as planning, organisation and attention and language processing covers vocabulary and comprehension. Episodic memory, working memory, and language processing are normally impaired in people with dementia. Fernández-Ballesteros et al. [321] measured overall cognition using the Digit-Symbol test from the Wechsler Adult Intelligence Score (WAIS [323]). The Digit-Symbol test predominantly evaluates components of executive function and has shown sensitivity to dementia [324], however, as an overall measure of cognition neglects to evaluate language or memory deficits. Hatch et al. [319] tested cognitive function using the National Adult Reading Test (NART [325]), a measure of language processing, and several tests developed within the British 1946 Birth Cohort study for verbal memory, verbal fluency and speed and concentration measuring working memory, language processing and executive function respectively but neglected episodic memory. Lenehan et al. used the WAIS, third edition, short form [326, 327] that included the picture completion, digit symbol coding, similarities and arithmetic components from the full WAIS together with the spelling and math computation components from the Wide Range Achievement Test (WRAT [328]). Together these covered working memory, executive function and language processing but neglected episodic memory. Several tests for each cognitive domain were used in Thow et al. [320]. The Logical Memory test [329], Rey Auditory Verbal Learning Test [330] and Paired Associates Learning [331] tested episodic memory. Digit Span [332], Letter-Number Sequencing [332], Spatial Span [331] and Spatial Working Memory [331] tested working memory. The Trail Making Test Trail B [333], 24-item Victoria version Stroop Colour-Word Test [333] and Rapid Visual Processing [331] tested executive function and language processing was tested by vocabulary [332], comprehension [332] and the Boston naming test [334]. Thow et al. had the most comprehensive cognitive tests for

individual cognitive domains [320] whilst Lenehan at al. had the most comprehensive test for global cognition but still did not cover episodic memory [322].

Table 7.2: Cognitive tests used in each study and the cognitive domains that each test covers

Study	**Cognitive tests**	**Cognitive Domains**			
		Episodic memory	Working memory	Executive function	Language processing
Fernández-Ballesteros et al. 2012	Digit-Symbol test from WAIS			X	
Hatch et al. 2007	NART				X
	Verbal memory		X		
	Verbal Fluency				X
	Speed and concentration			X	
Lenehan et al. 2016	WAIS-III Short Form and spelling and math computation components from WRAT		X	X	X
Thow et al. 2018	Logical memory test	X			
	Rey Auditory Verbal Learning Test	X			
	Paired Associates Learning	X			
	Digit Span		X		
	Letter-number sequencing		X		
	Spatial Span		X		
	Spatial working memory		X		
	Trail making test trail B			X	
	24-item Victoria version Stroop Colour-Word test			X	
	Rapid Visual Processing			X	
	Vocabulary				X
	Comprehension				X
	Boston Naming test				X

Methods to look at the association between lifelong education and cognition were necessarily different between studies depending on study design. Fernández-Ballesteros et al. [321] used a repeated measures ANCOVA adjusted for age and young adulthood education. Hatch et al. [319] used regression adjusted for sex, previous cognition, young adulthood education and social class

mobility with full information maximum likelihood (FIML) to account for missing data. Lenehan et al. [322] used growth mixture modelling on the control group and intervention group separately to identify subgroups on the basis of similar outcomes over time in cognition and adjusted for prior cognitive reserve which included young adulthood education. Thow et al. [320] used latent growth curve modelling, a type of growth mixture models, and adjusted for age and prior cognitive reserve (including young adulthood education). All studies adjusted for education in young adulthood.

Every study found an improvement in cognition or a cognitive domain when education was continued in later life. Cognition was measured before and after three years of university level education in the quasi-experimental group from the Fernández-Ballesteros et al. study. Those in the intervention group improved in cognition whereas cognition in the control group without later life education declined over the same period of time [321]. In the British 1946 birth cohort study [319] prospective analysis showed that any midlife education on top of young adulthood education improved verbal ability and verbal memory, even when adjusting for social class mobility. The association between later life education and verbal fluency was only present for those who completed some education with no resulting qualification in later life, in comparison to no later life education. Later life education was not associated with speed and concentration. When looking at overall cognition in the THBP [322] the control group and intervention group (with at least one year of university level study) were split into cognitive maintainers and improvers, in the control group 44.3% maintained cognitive function and 55.7% improved whereas in the intervention group 7.5% maintained cognitive function and 92.5% improved over four years of measurements. Looking at separate domains of cognition in the THBP [320] showed that language processing improved over the four year study period for the intervention group but remained stable for the control group. Episodic memory scores improved over four years for both the control and intervention group but there was no difference between the two groups. Working memory scores also improved over time for the control and intervention group but the improvement was only significant in the intervention group (although the intervention group was 3 times the size of the control group). Executive function remained stable in both groups over the four years.

7.4.3 Discussion

All studies on lifelong education and cognition included here found improved cognition for those who participated in later life education. Most research was on the association between lifelong education and specific cognitive domains but university education in later life was also shown to improve overall cognition.

To my knowledge this is the first attempt to synthesize the published evidence on lifelong education and cognition. The evidence reviewed included all languages and anything published up to June 2018. Although the inclusion criteria for lifelong learning were strict (excluding cognitive training and non-education measures of cognitive reserve such as social class), studies were not excluded based on methodology or design. There are some limitations to the interpretation of these results. Firstly only one database was searched and only one person screened the papers to decide on inclusion, although the Scopus database includes all articles from PubMed and more, some articles may have been missed. Whilst studies in other languages were not excluded, Scopus is an English database and the searched articles may be biased towards English written papers if other papers were only in non-English databases. The samples of the studies included were all from high income countries limiting the generalisability of these results to low and middle income countries. Only one of the studies was a representative sample of the population [319], other studies were unlikely to be representative owing to the small sample size and confounders could not be properly controlled for [321] or comprised of volunteers [320, 322]. Cognitive measures differed considerably between studies, including within each cognitive domain. The majority of these studies only considered university education in later life which requires a high level of prerequisite education to be eligible to enter. Those without high enough qualifications from young adulthood, who may benefit most from such interventions, were therefore less likely to be included in those studies. Another limitation is that although search terms for “lifelong learning” were as comprehensive as possible other terms may be used more commonly in other countries that have not been included.

Research evaluating the association of lifelong education with separate cognitive domains found later life education was associated with better language processing and working memory [319, 320]. Episodic memory improved in those who continued with education later in life [320],

however was only evaluated in one study. No evidence supporting an association between lifelong education and executive function was found [320]. There was variation in how particular tests were represented as measuring cognition. One of the studies used the Digit-Symbol test, usually a measure of executive function, as a measure of global cognition. Contradictory to results from studies explicitly assessing executive function through a composite measure [320], lifelong education was associated with improved Digit-Symbol test scores [321].

Overall cognition was only explicitly measured in one study [322]. Trends in overall cognition over time for the control and intervention group were separated into two groups – maintainers and improvers. Overall cognition improved in 55.7% and was maintained in 44.3% of the control group who received no further education, whereas in the intervention group who received at least one year of university level education overall cognition improved in 92.5% and was maintained in 7.5%. Improvements in overall cognition were seen in a far greater proportion of the intervention group in comparison to the control group, implying a protective association between lifelong education and cognition.

To address some of the areas of research that have not yet been covered the next part of this chapter concentrates on analysing the association between lifelong education at many different levels and overall cognition in mid and later life in a population representative study, the Cambridge Centre for Ageing and Neuroscience study. There was only one study that was population based and considered other forms of education later in life. However the study was on a birth cohort who had reached the age of 53 years and therefore associations between lifelong learning and cognition in later life could not be determined [319].

7.5 The Cambridge Centre for Ageing and Neuroscience Study

The Cambridge Centre for Ageing and Neuroscience study (CamCAN) is a large population based study that includes imaging measures [335]. The aim was to look at cognition across the lifespan. Primary Care Trust lists for the Cambridge City area were used to sample from everyone over the

age of 18 years. GPs were asked to exclude any patients they felt would be inappropriate due to terminal illness or risk to interviewer. A sample of 20,895 individuals was ascertained and 7,616 were eligible and approached [336]. Letters with an information sheet on the study and informing individuals that an interviewer would visit shortly were sent inviting eligible individuals to take part resulting in a sample size of 2,680 (35.2% response rate) for the Stage 1 interview [336]. After informed consent was given, an interview would be conducted in the participant's home with responses recorded on a computer. The interview consisted of questions on demographics, health and lifestyle. Cognitive function, balance, response time, hearing, vision, and medication use were also assessed. Before the interviewer arrived, participants were asked to complete The Lifetime of Experiences Questionnaire (LEQ [337]), slightly adjusted for the UK sample, and the European Prospective into Cancer Study-Norfolk Physical Activity Questionnaire (EPIC-EPAQ2 [338]). The self-completion questionnaire differed depending on the age of the participant. Those aged 18-29 years received a questionnaire with only the young adulthood section of the LEQ, whereas those aged 30-64 years received young adulthood and midlife sections of the LEQ and those aged 65 years or over received LEQ sections on young adulthood, midlife and later life.

Cognitive function was assessed in Stage 1 using the MMSE [85], the Addenbrooke's Cognitive Examination Revised (ACE-R – [339]), logical memory from the Wechsler Memory Scale Third UK edition (WMS-III UK – [340]), Spot the Word [341], and the Cambridge Memory Questionnaire (the Cambridge 10MQ). For comparison with both CFAS I and CFAS II the Cambridge Cognitive Examination (CAM-COG – [342]) and questions on activities of daily living were asked.

The baseline interview was also designed to test eligibility for entrance into Stage 2 of the study. To be able to take part in Stage 2 a participant must be cognitively healthy, be able to have Magnetic Resonance Imaging (MRI) and Magnetoencephalography (MEG) scans (have no magnetic objects in the body, such as pace makers or permanent dental braces, and could not be claustrophobic or pregnant), and must not have head injury, current psychiatric condition, hearing difficulties or poor English. A subsample of approximately 700 (100 per age decile 18 to 87 years) participants at Stage 1 were invited to participate in Stage 2, composed of a series of scans, further cognitive testing and physiological measures such as height, weight and blood pressure.

7.6 Analysis of lifelong education and cognition

7.6.1 Methods

The baseline home interview and self-completion questionnaires from CamCAN were used for this analysis. Three people with self-completion questionnaires but no home interview were excluded as they were term-time only students, outside the eligible sample for CamCAN. Analysis was restricted to those aged 55 years or older who had returned the self-completion questionnaire to enable the investigation of completed midlife education.

The ACE-R was administered at the home interview to measure cognition. Deprivation was measured by the Townsend deprivation index on post code and split into tertiles. The home interview asked for all the educational qualifications the participant had achieved in their life time and then coded as the highest achieved and grouped into university or equivalent, A level or equivalent, GCSE or equivalent and other qualifications (Table 7.3). Other variables from home interview included age (continuous then grouped into 18-27, 28-37, 38-47, 48-57, 58-67, 68-77, 78-87 and 88+ years), sex, marital status (married, single or widowed), social class (skilled, semi-skilled and unskilled, same as in CFAS I and II), self-perceived health (excellent, good, fair or poor). The questions from the home interview used for variables are in appendix A4.

As part of the LEQ the self-completion questionnaire asked about education at specific life stages including young adulthood (ages 13-29 years), midlife (ages 30-64 years) and later life (age 65 years or over). The self-completion questionnaire asked separately about each qualification at each life stage and qualifications were grouped as in Table 7.3. If the self-completion questionnaire had been returned but young adulthood education had not been completed then it was substituted from the home interview. If questions to midlife and later life qualifications were not answered then it was assumed that no midlife or later life education was completed.

Table 7.3: Qualifications asked in self-completion questionnaire and their equivalent grouping for analysis.

Education group for analysis	Qualifications
University/college degree or equivalent	College Undergraduate Masters PhD HNC/HND/NVQ4/BTEC-P BTEC-AD Other graduate qualification
A/AS levels or equivalent	A-level/International Baccalaureate NVQ3/BTEC-D
O-level/GCSE or equivalent	O-level/GCSE NVQ2/BTEC-1 CSE NVQ1/BTEC-I
Other	Clerical/book keeping course Business course Trade apprenticeship Other professional qualification Other technical qualification Other

Other life stage specific (young adulthood, midlife and later life) questions included travel (abroad, locally, never) and activities. Activities included: making an outing to see friends or family, playing a musical instrument, developing an artistic pastime (eg. drawing, acting, writing), mildly energetic activities, moderately energetic activities, vigorous energetic activities, reading, speaking a second language, playing computer games, social networking, crossword puzzles/Sudoku, strategic games (eg. chess) or prayer/religious activities. Each was split into frequency in taking part in the activity: never, less than weekly and at least weekly. If the self-completion questionnaire was returned but an activity question had not been answered it was assumed that the individual did not take part in the activity.

The self-completion questionnaire asked participants of all ages about employment. Employment was split into age groups 18-19, 20-24, 25-29, 30-34, 35-39, 40-44, 45-49, 50-54, 55-59, 60-64, 65-69, 70-74 and 75 and above years. Participants were asked to fill in a code from 1-10 (Table 7.4) responding to the Standard Occupation Classification most similar to their occupation in each of these age groups. The highest skilled occupation in young adulthood, midlife and later life was used for social class with categories skilled (codes 1-3), semi-skilled (codes 4-6), unskilled (codes

7-9) and not employed/retired (code 10). This grouping corresponds as much as possible to social class in CFAS I and CFAS II but was not identical. If the self-completion questionnaire was returned but the employment section had not been filled in it was assumed that the individual had been unemployed or retired.

Table 7.4: Codes for different occupations with examples

Code	Examples
1 – Managers and senior officials	Corporate managers: Directors, CEOs, parliamentarians, building and construction managers Specialist managers: Police officers (inspectors or above), officers in armed forces, hospital, finance, human resource, sales and marketing managers Other managers: Farm, shopkeepers, publicans, restaurant managers
2 – Professional occupations	Science, Building and Engineer professionals: Engineers, chemists, geologists, scientists, architects, surveyors Business and public service professionals: Solicitors, judges, accountants, auditors, marketing and advertising, librarians, architects, clergy Health professionals: Doctors, dentists, psychologists, optometrists, pharmacists, veterinarians Education professionals: Teachers, lecturers Social, arts and miscellaneous professionals: Social workers, counsellors, journalists, photographers, designers, illustrators
3 – Associate professionals and technical occupations	Science, Engineering: Technical officers, laboratory technicians, draughtspersons Business and Administration: Branch managers, finance dealers and brokers, office managers, computer support Health and welfare associate professionals: Nurses, midwives, physiotherapist, paramedics, youth and community workers Culture, media and sports: Artists, dancers, musicians, journalists, fitness instructors Business and public service: Air traffic controllers, pilots, train drivers, brokers, buyers Other associate professionals: Police officers (sergeant and below), fire service (leading fire officer and below)
4 – Administrative and secretarial occupations	Administrative occupations: Counter clerks, civil service officers, telephonists Secretarial: Secretaries (all types), typists, personal assistants
5 – Skilled trades occupations	Agricultural, metal and electrical: Farmers, gardeners, smiths, sheet metal workers, mechanics, electricians Building trade: Bricklayers, roofers, plumbers, carpenters, plasterers Other trades: Tailors, printers, butchers, bakers, chefs, floral arrangers

Code	Examples
6 – Personal service occupations	Caring personal service: Nursing assistants, ambulance staff, dental nurses, childminders, teaching assistants, veterinary nurses, care assistants Leisure and other personal service: Travel agents, tour guides, sports assistants, hairdressers, housekeepers, pest control officers
7 – Sales and Customer service occupations	Sales: Sales assistants, market traders, debt collectors Customer service: Call centre agents, customer care occupations
8 – Process, plant and machine operatives	Process, plant and construction: Food, drink, chemical, plastic process operatives, machine operatives, assemblers, windscreen fitters, scaffolders, rail maintenance workers Transport and mobile machine drivers: Heavy goods vehicle, van, bus, taxi drivers, merchant navy, crane drivers
9 – Elementary occupations	Agricultural, construction, goods: Farm, forestry workers, labourers, packers, dockers Personal service, administration: Postal workers, porters, waiters, waitresses, bar staff Cleaning, security and sales: Window cleaners, refuse occupations, security guards, traffic wardens, shelf fillers
10 – Retired or not employed	

Previous analysis showed inverse probability weights were needed for the baseline home interview [336]. Inverse probability weights for the baseline home interview included age, sex and deprivation. The self-completion questionnaire was conducted at the same time as the baseline home interview but was only returned by a subsample of the participants. The subsample who returned the self-completion questionnaire differed slightly to the participants who completed the baseline home interview in the main measures of interest. The subsample who returned their self-completion questionnaire were more likely to have higher cognition and higher education. The subsample that returned the self-completion questionnaires were therefore inverse probability weighted for education and MMSE group. To account for differences in demographics and health the self-completion questionnaire inverse probability weights also included age, sex, deprivation, marital status, social class and self-perceived health.

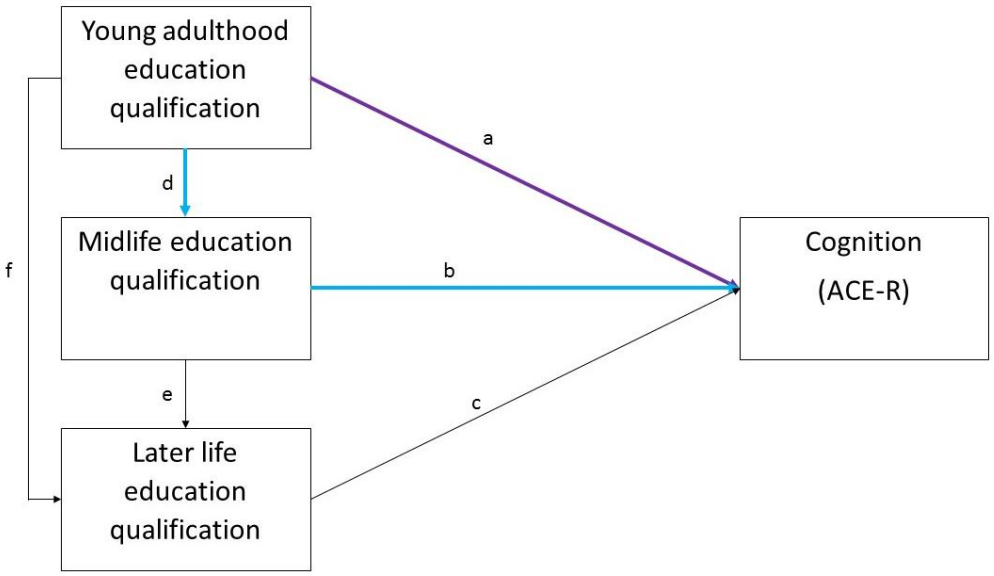
Table 7.5: Covariates considered for each model

	Model 1	**Model 2**	**Model 3**	**Model 4**
Education	Young adulthood education Midlife education Later life education	Young adulthood education Midlife education Later life education	Young adulthood education Midlife education Later life education	Young adulthood education Midlife education Later life education
Covariates from home interview (not life stage specific)		Age Sex Deprivation Social class Marital status Self-perceived health	Age Sex Deprivation Marital status Self-perceived health	Age Sex Deprivation Marital status Self-perceived health
Covariates from self-completion questionnaire (life stage specific in young adulthood, midlife and later life)			Occupation Travel Seeing family or friends Playing a musical instrument Practicing an artistic pastime Mild energetic activity Moderate energetic activity Vigorous energetic activity Reading Speaking another language Computer games Social networking Puzzles Strategic games Religious activity	Occupation Travel Seeing family or friends Playing a musical instrument Practicing an artistic pastime Mild energetic activity Moderate energetic activity Vigorous energetic activity Reading Speaking another language Computer games Social networking Puzzles Strategic games Religious activity

An unadjusted weighted path analysis as pictured in Figure 7.2 was used to observe the association between education in young adulthood, midlife and later life and cognition measured

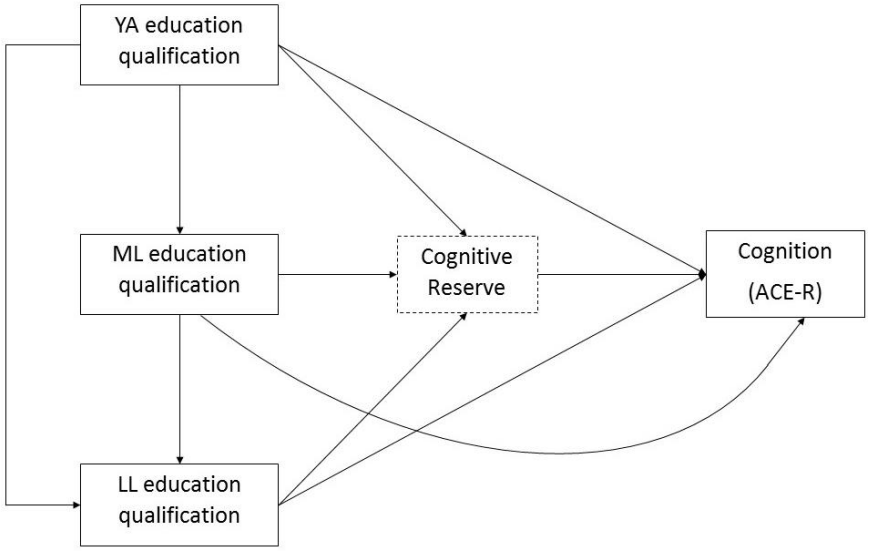
by the ACE-R. Each pathway a, b, c, d, e and f was tested individually using linear regression if the outcome was continuous or multinomial logistic regression for categorical outcomes before the complete path analysis was analysed (Model 1). See Table 7.5 for covariates considered in each model. Path analysis can measure direct and indirect associations between variables and outcomes. Figure 7.2 shows the direct association of young adulthood education with cognition (Figure 7.2 purple arrow) and one of the indirect associations between young adulthood education and cognition (Figure 7.2 blue arrows). An example of the direct association would be if higher young adulthood education was associated with better cognition (Figure 7.2 path a). An example of the indirect association would be if completing higher young adulthood education was associated with completing any midlife education (path d) and completing a qualification in midlife was associated with better cognition (path b). Therefore young adulthood education could be both directly and indirectly associated with cognition (both path a and path d, b are important) or only directly (only path a is important) or only indirectly (only path d, b is important) associated with cognition. There are also other indirect associations between young adulthood education and cognition, for instance f, c and d, e, c.

Figure 7.2: Path analysis for the association between midlife or later life education and cognitive function. Purple arrow describes direct association between young adulthood education and cognition. One indirect association between young adulthood eductaion and cognition could be described by the blue arrows.



Covariates from the home interview that were not life stage specific (Table 7.5) were then added to the model (Model 2) by modelling each pathway first before the complete path analysis. The same process was followed when adding life-point specific cognitive reserve variables from the self-completion questionnaire as covariates (Model 3, Table 7.5). As cognitive reserve cannot be measured in itself, only by proxies, a Structural Equation Model (SEM) with latent construct for cognitive reserve was also considered (Model 4 – Figure 7.3) using the same variables considered in Model 3 (Table 7.5). Any of the specific life stage cognitive reserve variables that were associated with cognition in multivariate analysis were included in the latent variable. As cognitive reserve is also normally developed by further education, the latent variable was considered as a mediator between education and cognitive reserve.

Figure 7.3: SEM with cognitive reserve as a latent mediator



Fit measures for weighted GSEM were limited in Stata. Overall model fit indices such as the AIC or BIC were not available as inverse probability weighting violates the maximum likelihood assumption that cases are independent. Modification indices were only available for SEM and not GSEM in Stata. To determine whether paths should remain in the full model, Wald tests were conducted on individual categories of variables and also on variables as a whole.

7.6.2 Results

There were 2,680 participants in the CamCAN baseline home interview. After excluding those who did not return the self-completion questionnaire and anyone below the age of 55 years 1,148 individuals remained in the analysis. Table 7.6 gives the number and percentage of participants with demographic and health variables from the home interview. Mean age was 74 years and 57% were women (Table 7.6). Education from the home interview was the highest the participant had achieved so far in their lifetime, with 42.4% having university level education (Table 7.6). Cognition was measured at the home interview by the ACE-R, with scores between 0 and 100 and the mean was 89.7 (Table 7.6).

Table 7.6: Demographic, health and cognitive reserve factors from CamCAN home interview and self-completion questionnaire

		n	Weighted %	95% CI
Age group	55-64	261	17.6	15.6 – 19.8
	65-74	281	19.2	17.1 – 21.5
	75-84	421	39.0	36.0 – 42.2
	≥85	185	24.2	21.1 – 27.5
Sex	Men	519	43.4	40.3 – 46.5
	Women	629	56.6	53.5 – 59.8
Deprivation	Least deprived	488	37.2	34.2 – 40.3
	Middle deprived	395	33.4	30.4 – 36.4
	Most deprived	265	29.5	26.5 – 32.6
Education	Other	315	34.4	31.2 – 37.7
	GCSE	184	15.2	13.1 – 17.6
	A-level	89	8.0	6.4 – 9.9
	University	553	42.4	39.4 – 45.6
Social class	Skilled	620	49.4	46.2 – 52.6
	Semi-skilled	405	39.0	35.9 – 42.2
	Unskilled	105	11.6	9.5 – 14.1
Marital status	Married	632	49.9	46.7 – 53.1
	Single	239	20.0	17.6 – 22.6
	Widowed	275	30.2	27.1 – 33.4
Self-perceived health	Excellent	301	24.7	22.1 – 27.4
	Good	615	53.8	50.6 – 57.0
	Fair	183	16.9	14.6 – 19.5
	Poor	41	4.7	3.3 – 6.5
Cognition	ACE-R	1148	Mean: 89.7	SD: 9.7

Education and cognitive reserve variables that were used in the path analysis and SEMs were from specific life stages. Table 7.7 gives the number and percentage of participants with these variables in young adulthood, midlife and later life. Everyone had achieved an educational qualification in young adulthood (Table 7.7), 35.1% received an educational qualification in midlife and 9.1% received an educational qualification in later life. Although all levels of qualifications are included in the self-completion questionnaire, qualifications were merged to ensure sufficient numbers in each group when assessing covariates to be included in the model. In midlife university or other qualifications were compared with no or less than university midlife qualifications and in later life other qualifications were compared to no or some later life formal educational qualifications (Table 7.7). The majority of participants had skilled occupations in young adulthood and the majority had skilled occupations in midlife (Table 7.7). In later life this shifted to the majority being unemployed or retired (Table 7.7).

Table 7.7: Young adulthood education and cognitive reserve variables from the self-completion questionnaire

		Young adulthood			Midlife			Later life		
		n	Weighted %	95% CI	n	Weighted %	95% CI	n	Weighted %	95% CI
Education	None	NA			704	64.8	61.8 – 67.8	1036	90.9	89.0 – 92.5
	Other	330	35.3	32.1 – 38.5	221	18.6	16.3 – 21.3	90	7.5	6.0 – 9.3
	GCSE	190	16.2	14.0 – 18.7	30	2.4	1.6 – 3.6	4	0.3	0.1 – 0.9
	A-level	82	6.8	5.4 – 8.7	14	1.1	0.6 – 1.8	1	0.1	0.0 – 0.7
	University	544	41.7	38.7 – 44.8	177	13.0	11.2 – 15.1	15	1.2	0.7 – 2.0
Occupation	Skilled	629	50.6	47.4 – 53.8	706	55.9	52.6 – 59.1	156	12.0	10.2 – 14.1
	Semi-skilled	298	27.9	25.0 – 30.9	249	23.8	21.1 – 26.7	57	5.1	3.9 – 6.7
	Unskilled	83	7.6	6.1 – 9.5	69	7.6	5.9 – 9.7	34	3.7	2.6 – 5.4
	Unemployed/retired	137	13.9	11.7 – 16.4	123	12.8	10.6 – 15.3	899	79.2	76.5 – 81.6
Travel	Abroad	809	64.8	61.5 – 67.9	950	79.9	77.0 – 82.5	623	55.7	52.5 – 58.8
	Locally	175	17.6	15.1 – 20.3	71	7.3	5.7 – 9.2	111	10.9	9.0 – 13.2
	None	164	17.7	15.1 – 20.5	127	12.8	10.7 – 15.3	413	33.4	30.5 – 36.4
Seeing family or friends	At least weekly	630	52.4	49.2 – 55.6	635	53.6	50.4 – 56.8	443	38.7	35.7 – 41.9
	Less than weekly	384	33.6	30.7 – 36.7	411	35.5	32.5 – 38.7	353	33.2	30.2 – 36.4
	Never	133	14.0	11.7 – 16.6	102	10.9	8.8 – 13.3	352	28.0	25.3 – 31.0
Play musical instrument	At least weekly	334	27.9	25.1 – 30.8	153	13.0	11.0 – 15.2	72	6.1	4.7 – 7.7
	Less than weekly	101	7.8	6.3 – 9.5	117	9.1	7.5 – 10.9	70	6.0	4.7 – 7.7
	Never	712	64.4	61.3 – 67.4	877	78.0	75.3 – 80.4	1005	87.9	85.8 – 89.8
Practise artistic pastime	At least weekly	276	22.9	20.3 – 25.6	263	22.1	19.6 – 24.8	203	17.8	15.5 – 20.4
	Less than weekly	214	17.6	15.3 – 20.0	203	16.6	14.4 – 19.0	116	10.7	8.8 – 12.8
	Never	656	59.6	56.5 – 62.7	681	61.3	58.2 – 64.4	829	71.5	68.5 – 74.3
Mildly energetic activity	At least weekly	903	77.7	74.9 – 80.3	963	82.3	79.5 – 84.7	709	63.6	60.4 – 66.6
	Less than weekly	96	7.8	6.3 – 9.6	84	7.3	5.9 – 9.1	80	8.2	6.5 – 10.3
	Never	148	14.5	12.2 – 17.0	100	10.4	8.4 – 12.8	359	28.3	25.6 – 31.2
Moderately energetic activity	At least weekly	779	66.1	63.0 – 69.1	782	66.8	63.7 – 69.8	480	41.5	38.4 – 44.7
	Less than weekly	175	14.0	12.0 – 16.2	198	16.7	14.5 – 19.1	171	16.1	13.8 – 18.8
	Never	194	19.9	17.3 – 22.8	167	16.5	14.2 – 19.2	497	42.4	39.2 – 45.6
Vigorous energetic activity	At least weekly	389	31.4	28.6 – 34.4	251	19.3	17.0 – 21.8	88	7.3	5.9 – 9.0
	Less than weekly	197	15.4	13.4 – 17.7	191	14.7	12.7 – 16.9	47	3.8	2.8 – 5.1
	Never	560	53.2	50.0 – 56.3	706	66.0	63.0 – 68.9	1013	88.9	86.9 – 90.7

		Young adulthood			Midlife			Later life		
		n	Weighted %	95% CI	n	Weighted %	95% CI	n	Weighted %	95% CI
Reading	At least weekly	1004	85.8	83.2 – 88.0	1021	87.5	84.5 – 89.6	775	70.7	67.8 – 73.5
	Less than weekly	41	3.7	2.6 – 5.0	34	3.1	2.2 – 4.5	23	1.9	1.3 – 3.0
	Never	103	10.6	8.6 – 12.9	93	9.4	7.6 – 11.7	349	27.4	24.7 – 30.2
Speak another language	At least weekly	247	20.9	18.4 – 23.6	204	16.2	14.1 – 18.6	114	9.9	8.1 – 11.9
	Less than weekly	241	17.5	15.4 – 19.9	267	20.5	18.2 – 23.0	164	13.0	11.1 – 15.2
	Never	659	61.6	58.5 – 64.6	677	63.3	60.3 – 66.3	869	77.1	74.4 – 79.7
Computer games	At least weekly	17	1.6	1.0 – 2.7	93	6.9	5.6 – 8.5	80	7.2	5.7 – 9.1
	Less than weekly	42	3.0	2.1 – 4.1	83	6.0	4.8 – 7.5	35	2.8	2.0 – 4.0
	Never	1088	95.4	94.0 – 96.5	971	87.1	85.1 – 88.9	1032	90.0	87.9 – 91.7
Social networking	At least weekly	38	3.4	2.3 – 4.8	305	21.6	19.3 – 24.1	231	19.0	16.7 – 21.6
	Less than weekly	16	1.4	0.8 – 2.4	52	3.8	2.9 – 5.0	44	3.8	2.8 – 5.2
	Never	1093	95.3	93.6 – 96.5	790	74.6	71.9 – 77.1	872	77.2	74.4 – 79.7
Crossword puzzles/sudoku	At least weekly	310	27.7	24.9 – 30.7	490	41.8	38.7 – 45.0	448	40.0	36.9 – 43.2
	Less than weekly	208	16.4	14.3 – 18.7	165	13.1	11.2 – 15.3	79	7.6	6.0 – 9.5
	Never	629	55.9	52.7 – 59.0	492	45.0	41.8 – 48.3	620	52.5	49.3 – 55.7
Strategic games	At least weekly	79	6.6	5.2 – 8.3	50	4.2	3.1 – 5.6	48	4.1	3.1 – 5.5
	Less than weekly	363	28.4	25.7 – 31.3	270	20.5	18.2 – 23.0	135	10.9	9.2 – 13.0
	Never	704	65.0	62.0 – 67.9	827	75.3	72.6 – 77.8	964	85.0	82.6 – 87.0
Prayer/religious activity	At least weekly	413	36.3	33.2 – 39.4	316	27.7	24.9 – 30.7	258	23.9	21.2 – 26.8
	Less than weekly	217	18.1	15.8 – 20.6	194	16.6	14.4 – 19.1	129	11.3	9.5 – 13.5
	Never	517	45.7	42.5 – 48.9	637	55.7	52.5 – 58.8	760	64.8	61.6 – 67.8

After unadjusted models to examine each pathway separately (Figure 7.4), the pathway between young adulthood qualification and later life qualification (path f) looked unimportant. However, as this was the unadjusted model all paths were retained until adjusting for confounders such as age and sex. Fitting all pathways in Figure 7.4 both young adulthood education and midlife education were associated with cognition directly (path a and path b respectively). Young adulthood education was directly associated with cognition (Figure 7.4 path a), as well as having an indirect association through midlife education (Figure 7.4 path d, b). The direct association shows that those who gained university level education in young adulthood had better cognition in comparison to those who gained other qualifications or GCSEs in young adulthood. The indirect association between young adulthood education and cognition through midlife education showed that those with higher education in young adulthood were more likely to complete university in midlife (results not shown) who had better cognition in comparison to those who did not do any education in midlife (Table 7.8).

Figure 7.4: Unadjusted path analysis for lifelong education and cognition

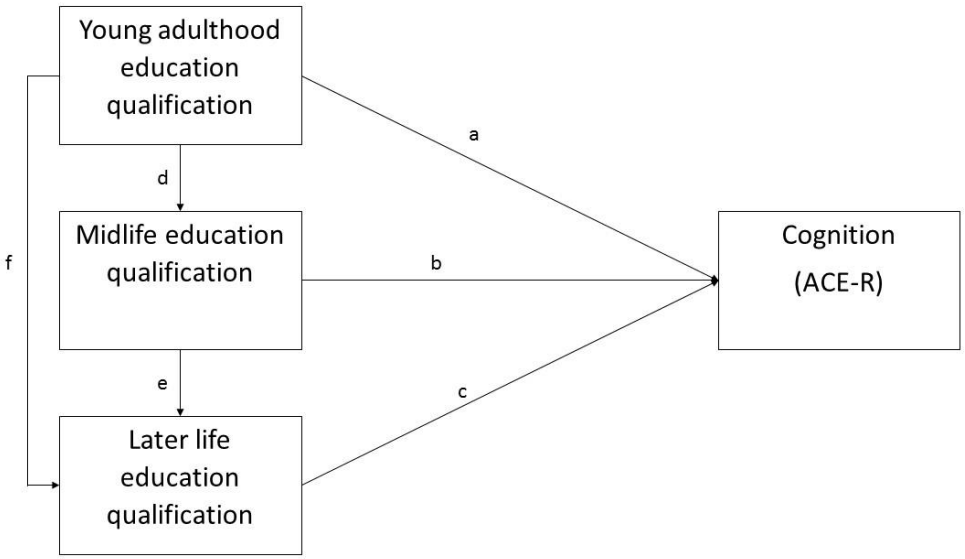


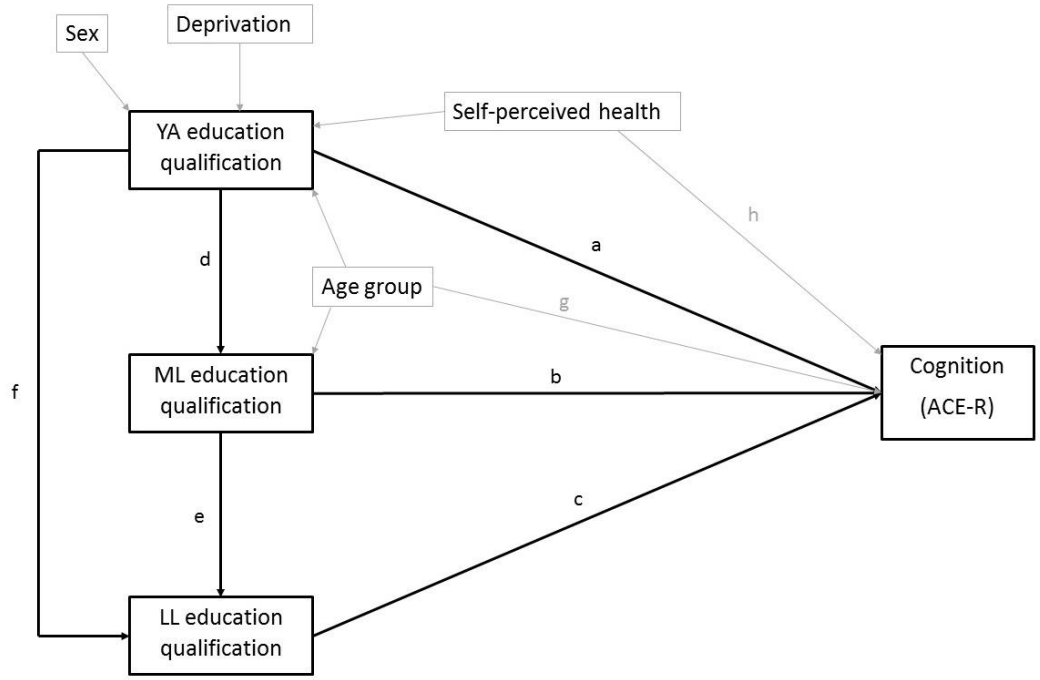
Table 7.8: Results from path analysis and SEMs for paths where cognition (ACE-R) is outcome. Model 1 is for unadjusted path analysis. Model 2 adjusts for covariates at home interview. Model 3 adjusts for covariates at the home interview and life stage specific cognitive reserve variables. Model 4 adjusts for covariates from the home interview and cognitive reserve is a latent construct. Ref refers to reference category.

Outcome: ACE-R		**Model 1**		**Model 2**		**Model 3**		**Model 4**	
		Coeff.	95% CI	Coeff.	95% CI	Coeff.	95% CI	Coeff.	95% CI
Young adulthood education	Other	-7.9	-9.3 – -6.4	-6.0	-7.4 – -4.6	-4.0	-5.4 – -2.5	-4.0	-5.4 – -2.5
(path a)	GCSE	-2.8	-4.4 – -1.2	-1.8	-3.3 – -0.4	-1.1	-2.7 – 0.5	-1.1	-2.7 – 0.5
	A-level	-2.3	-6.2 – 1.6	-2.0	-4.8 – 0.9	-1.7	-4.2 – 0.7	-1.7	-4.2 – 0.7
	University	ref	-	ref	-	ref	-	ref	-
Midlife education	None/GCSE/A-level	ref	-	ref	-	ref	-	ref	-
(path b)	Other	0.9	-0.9 – 2.6	0.7	-0.8 – 2.1	-0.2	-1.5 – 1.1	-0.2	-1.5 – 1.1
	University	2.8	1.4 – 4.3	1.2	-0.1 – 2.5	0.4	-0.8 – 1.6	0.4	-0.8 – 1.6
Later-life education	None/GCSE/A-level/University	ref -	-	ref	-	ref	-	ref	-
(path c)	Other	1.9	-0.1 – 3.9	3.0	1.1 – 4.9	2.0	0.2 – 3.7	2.0	0.2 – 3.7
Age group	55-64			4.6	3.3 – 5.9	7.1	5.0 – 9.2	7.1	5.0 – 9.2
(path g)	65-74			3.4	2.3 – 4.6	2.6	1.6 – 3.7	2.6	1.6 – 3.7
	75-84			ref	-	ref	-	ref	-
	≥85			-4.4	-6.3 – -2.6	-3.8	-5.5 – -2.1	-3.8	-5.5 – -2.1
Self-perceived health	Excellent			ref	-	ref	-	ref	-
(path h)	Good			-0.7	-1.9 – 0.5	-0.6	-1.7 – 0.4	-0.6	-1.7 – 0.5
	Fair			-2.3	-4.0 – -0.6	-1.9	-3.5 – -0.2	-1.9	-3.5 – -0.2
	Poor			-5.4	-9.8 – -1.0	-5.7	-9.5 – -1.9	-5.7	-9.5 – -1.9
COGNITIVE RESERVE – OCCUPATION									
Young adulthood occupation	Skilled					ref	-		
	Semi-skilled					-0.2	-1.6 – 1.3		
(path i1)	Unskilled					-0.5	-2.8 – 1.8		
	Unemployed/retired					-2.6	-4.4 – -0.9		

Outcome: ACE-R		**Model 1**		**Model 2**		**Model 3**		**Model 4**	
		Coeff.	95% CI	Coeff.	95% CI	Coeff.	95% CI	Coeff.	95% CI
Later life occupation	Skilled					2.2	0.9 – 3.4		
(path j3)	Semi-skilled					0.2	-2.3 – 2.7		
	Unskilled					-2.8	-5.5 – -0.1		
	Unemployed/retired					ref	-		
COGNITIVE RESERVE – OTHER									
Young adulthood music	At least weekly					1.9	0.7 – 3.1		
(path i2)	Less than weekly					1.2	-0.02 – 2.4		
	Never					ref	-		
Young adulthood family and	At least weekly					ref	-		
friends	Less than weekly					-0.6	-1.7 – 0.6		
(path j2)	Never					-2.3	-4.2 – -0.4		
Young adulthood board	At least weekly					-0.6	-2.5 – 1.2		
games	Less than weekly					1.2	0.2 – 2.2		
(path i3)	Never					ref	-		
Young adulthood vigorous	At least weekly					ref	-		
activity	Less than weekly					0.3	-0.7 – 1.3		
(path j1)	Never					-2.0	-3.1 – -0.8		
Later life moderate activity	At least weekly					ref	-		
(path j4)	Less than weekly					1.4	-0.1 – 2.8		
	Never					-1.8	-3.4 – -0.2		
Later life puzzles	At least weekly					3.0	1.7 – 4.2		
(path j5)	Less than weekly					0.8	-1.4 – 3.0		
	Never					ref	-		

Adding covariates to the model results in Model 2 shown in Figure 7.5. After adjusting for age, young adulthood education remained associated with cognition, higher young adulthood education was associated with better cognition (Table 7.8, Figure 7.5 path a). Later life education was associated directly with cognition as well, completing other qualifications in later life was associated with better cognition (Figure 7.5 path c). Midlife education was no longer directly associated with cognition (Table 7.8, Figure 7.5 path b) but was indirectly associated with cognition through later life education (Figure 7.5 path e, c) as completing any midlife education increased the likelihood of completing other qualifications in later life (results not shown). There were indirect associations between young adulthood education and cognition through midlife education then later life education (Figure 7.5 path d, e, c) and also on its own through later life education (Figure 7.5 path f, c). The indirect association between young adulthood education and cognition through later life education meant that those who completed higher education in young adulthood were more likely to complete other qualifications in later life (results not shown), in turn associated with better cognition (Table 7.8, Figure 7.5 path f, c). The indirect association between young adulthood education and cognition through midlife education and later life education showed that young adulthood education was associated with the choice to continue with education in midlife (Figure 7.5 path d) which in turn was associated with the choice to continue education in later life (Figure 7.5 path e). Self-perceived health was associated with cognition, those who had fair or poor self-perceived health had lower cognition than those with excellent self-perceived health. Sex and deprivation were associated with young adulthood qualification, being a woman or more deprived increased the likelihood of having lower young adulthood qualifications.

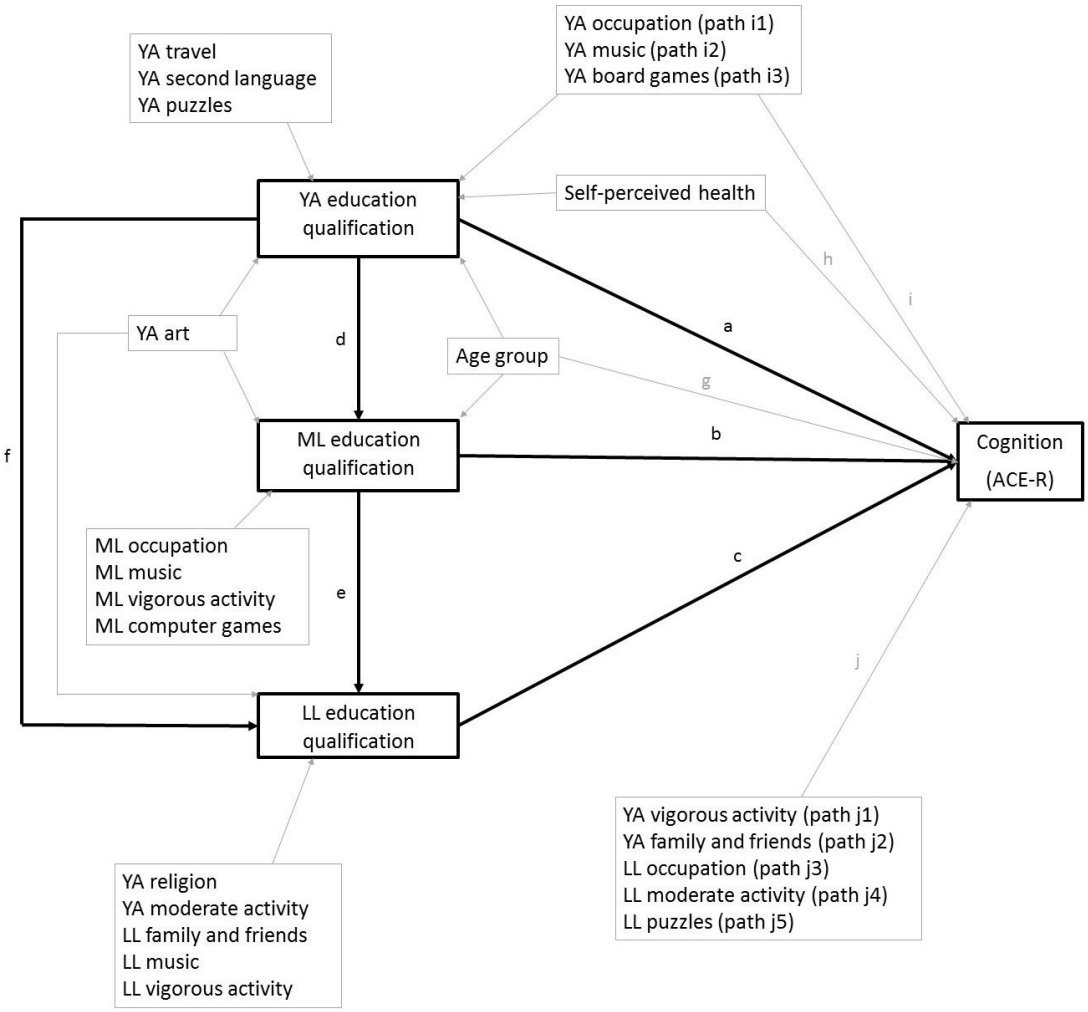
Figure 7.5: Adding covariates but not cognitive reserve to the path analysis. Bold marks the structural model and grey marks the covariates. YA stands for young adulthood, ML stands for midlife and LL stands for later life.



Adding cognitive reserve variables to the path analysis as covariates resulted in Model 3 as shown in Figure 7.6. After adjusting for cognitive reserve covariates young adulthood education and later life education were both still associated with cognition directly but the associations were not as strong (Table 7.8). The direct association between young adulthood education and cognition showed that that those who gained university level qualifications in young adulthood had better cognition than those who had other qualifications in young adulthood. Again, the indirect association between young adulthood education and cognition through later life education (results not shown) found that those who continued with education in later life after young adulthood education and gained other qualifications had better cognition than those who did no or some later life education. Self-perceived health was still associated with cognition (Table 7.8). Both young adulthood occupation and later life occupation were associated with cognition (Table 7.8). Being unemployed (or retired) in young adulthood was associated with poorer cognition and being in a skilled occupation in later life in comparison to being retired (or unemployed) was associated with better cognition. Other cognitive reserve variables associated with cognition

included playing a musical instrument in young adulthood, playing board games in young adulthood, vigorous physical activity in young adulthood, seeing family and friends in young adulthood, doing puzzles in later life and moderate physical activity in later life.

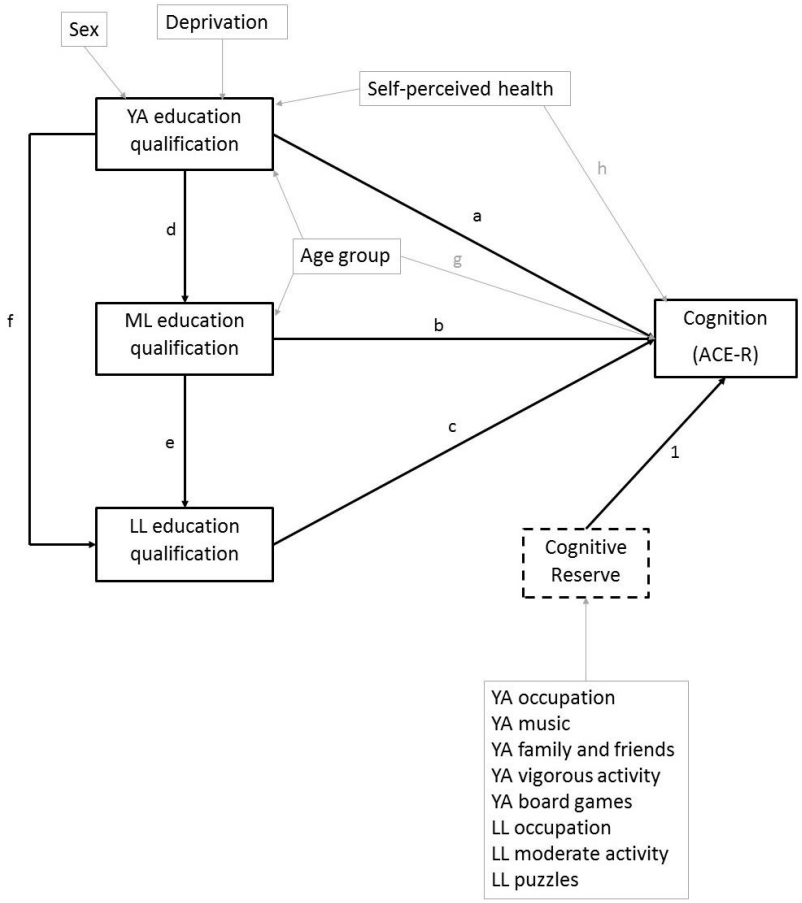
Figure 7.6: Adding covariates and cognitive reserve variables to the path analysis. Bold marks the structural model and grey marks the covariates. YA stands for young adulthood, ML stands for midlife and LL stands for later life.



Cognitive reserve was considered a latent mediator between further education and cognition (Figure 7.3), however the model lacked identification. The addition of more paths without adding more covariates caused instabilities, constraints could be applied however as the main outcome of interest was education at different life stages on cognition these paths could not be constrained. Adding more variables to the model (the covariates from Model 2) made the

variance-covariance matrix become highly singular and standard errors could not be estimated. The latent SEM considered (Model 4) is shown in Figure 7.7. Stata constrains the path between the latent cognitive reserve variable and cognition to one and the error variance of ACE-R was constrained to enable model identification. The estimates of the effects on cognition of latent cognitive reserve were the same as for Model 3 when cognitive reserve variables were included as covariates (Table 7.8). Even when fully adjusting for cognitive reserve young adulthood education was still associated directly with cognition (Table 7.8). Young adulthood education was also associated with cognition indirectly through midlife and later life education (Table 7.9) with those completing university level education in young adulthood more likely to go on to complete any midlife education and other later life education (Table 7.9). Midlife education was associated with cognition through later life education (Table 7.9) and later life education was associated with cognition directly (Table 7.8).

Figure 7.7: SEM with latent cognitive reserve. Bold marks the structural model and grey marks the covariates. YA stands for young adulthood, ML stands for midlife and LL stands for later life. Dotted line indicates latent variable.



In order to determine whether paths should remain in Model 4, Wald tests were conducted for individual categories and overall variables, the results of which are in Table 7.9. Whereas Table 7.8 only gives the results for paths with cognition as the outcome, Table 7.9 holds the results for all the paths in Model 4, including a repetition of the results with cognition as the outcome. The path between midlife education and cognition could be removed from the model, but since this is the specific association studied it has remained in the model (Table 7.9). In some cases it is difficult to determine whether or not the paths should remain in the model. This is when, for a multinomial outcome the variable is important to one of the categories of the multinomial outcome but not for the others, for instance with midlife education as the outcome age group is not important to the other qualifications category but is important to the university category (Table 7.9). In these cases, given the strength of the association in one category the variables have remained in the model.

Table 7.9: Results for all paths in Model 4 with either relative risk ratio (RR) if the outcome was multinomial, odds ratio (OR) if outcome was binary or coefficient (coeff.) if outcome was continuous and the corresponding 95% confidence interval (CI) and Wald p-value for individual categories of the risk factors. P-values for the risk factor overall are given in the reference category of the risk factor.

OUTCOME: YA education other vs. university				
		RR	**95% CI**	**P-value**
Age group	55-64	0.2	0.1 – 0.3	0.000
	65-74	0.5	0.4 – 0.8	0.001
	75-84	ref	-	0.000
	85+	1.5	1.0 – 2.4	0.047
Sex	Woman	1.2	0.9 – 1.6	0.311
Deprivation tertiles	Least deprived	ref	-	0.025
	Middle deprived	1.6	1.1 – 2.2	0.017
	Most deprived	1.6	1.1 – 2.3	0.027
Self-perceived health	Excellent	ref	-	0.001
	Good	2.1	1.4 – 3.2	0.000
	Fair	2.2	1.3 – 3.7	0.003
	Poor	2.7	1.1 – 6.6	0.028
OUTCOME: YA education GCSE vs. university				
		RR	**95% CI**	**P-value**
Age group	55-64	0.7	0.4 – 1.1	0.121
	65-74	1.4	0.9 – 2.3	0.139
	75-84	ref	-	0.002
	85+	1.9	1.1 – 3.2	0.022
Sex	Woman	2.0	1.4 – 2.9	0.000
Deprivation tertiles	Least deprived	ref	-	0.667
	Middle deprived	1.1	0.7 – 1.6	0.792
	Most deprived	1.2	0.8 – 2.0	0.370
Self-perceived health	Excellent	ref	-	0.332
	Good	0.9	0.6 – 1.4	0.698
	Fair	1.4	0.8 – 2.5	0.207
	Poor	1.5	0.5 – 3.9	0.449
OUTCOME: YA education A-level vs. university				
		RR	**95% CI**	**P-value**
Age group	55-64	0.7	0.3 – 1.3	0.227
	65-74	1.2	0.7 – 2.2	0.525
	75-84	ref	-	0.255
	85+	0.6	0.2 – 1.7	0.346
Sex	Woman	1.8	1.1 – 3.1	0.030
Deprivation tertiles	Least deprived	ref	-	0.284
	Middle deprived	1.0	0.6 – 1.7	0.918
	Most deprived	0.6	0.3 – 1.2	0.128
Self-perceived health	Excellent	ref	-	0.111
	Good	0.8	0.4 – 1.3	0.339
	Fair	1.2	0.6 – 2.5	0.684
	Poor	3.4	1.0 – 12.4	0.059

OUTCOME: ML education Other vs. None/GCSE/A-level

		RR	95% CI	P-value
YA qualification	Other	0.4	0.2 – 0.6	0.000
	GCSE	0.9	0.6 – 1.4	0.773
	A-level	0.6	0.3 – 1.4	0.241
	Uni	ref	-	0.000
Age group	55-64	1.4	1.0 – 2.1	0.082
	65-74	1.2	0.8 – 1.8	0.411
	75-84	ref	-	0.381
	85+	1.1	0.7 – 1.8	0.659

OUTCOME: ML education university vs. None/GCSE/A-level

		RR	95% CI	P-value
YA qualification	Other	0.04	0.01 – 0.10	0.000
	GCSE	0.3	0.2 – 0.6	0.000
	A-level	0.9	0.5 – 1.6	0.692
	Uni	ref	-	0.000
Age group	55-64	2.1	1.3 – 3.3	0.002
	65-74	1.9	1.2 – 3.1	0.011
	75-84	ref	-	0.000
	85+	0.4	0.2 – 0.9	0.037

OUTCOME: LL education other vs. none/GCSE/A-level/university

		OR	95% CI	P-value
YA qualification	Other	0.3	0.2 – 0.7	0.006
	GCSE	0.6	0.3 – 1.1	0.102
	A-level	1.3	0.6 – 3.1	0.527
	University	ref	-	0.022
ML qualification	None/GCSE/A-level	ref	-	0.000
	Other	5.6	3.2 – 9.9	0.000
	University	2.2	1.0 – 4.8	0.044

OUTCOME: ACE-R (Same as in Table 7.8)

		Coeff.	95% CI	P-value
Young adulthood education	Other	-4.0	-5.4 – -2.5	0.000
	GCSE	-1.1	-2.7 – 0.5	0.174
	A-level	-1.7	-4.2 – 0.7	0.169
	University	ref	-	0.000
Midlife education	None/GCSE/A-level	ref	-	0.662
	Other	-0.2	-1.5 – 1.1	0.757
	University	0.4	-0.8 – 1.6	0.495
Later-life education	None/GCSE/A-level/University	ref	-	
	Other	2.0	0.2 – 3.7	0.031
Age group	55-64	7.1	5.0 – 9.2	0.000
	65-74	2.6	1.6 – 3.7	0.000
	75-84	ref	-	0.000
	≥85	-3.8	-5.5 – -2.1	0.000
Self-perceived health	Excellent	ref	-	0.007
	Good	-0.6	-1.7 – 0.5	0.259
	Fair	-1.9	-3.5 – -0.2	0.032
	Poor	-5.7	-9.5 – -1.9	0.004
Cognitive reserve (latent)	RESTRAINED	1.0		

OUTCOME: Cognitive Reserve (latent)

		Coeff.	95% CI	P-value
YA occupation	Skilled	ref	-	0.029
	Semi-skilled	-0.2	-1.6 – 1.3	0.807
	Unskilled	-0.5	-2.8 – 1.8	0.676
	Unemployed/retired	-2.6	-4.4 – -0.9	0.003
LL occupation	Skilled	2.2	0.9 – 3.4	0.001
	Semi-skilled	0.2	-2.3 – 2.7	0.884
	Unskilled	-2.8	-5.5 – -0.1	0.043
	Unemployed/retired	ref	-	0.001
YA music	At least weekly	1.9	0.7 – 3.1	0.001
	Less than weekly	1.2	-0.02 – 2.4	0.054
	Never	ref	-	0.005
YA family and friends	At least weekly	ref	-	0.049
	Less than weekly	-0.6	-1.7 – 0.6	0.329
	Never	-2.3	-4.2 – -0.4	0.016
YA board games	At least weekly	-0.6	-2.5 – 1.2	0.490
	Less than weekly	1.2	0.2 – 2.2	0.014
	Never	ref	-	0.019
YA vigorous activity	At least weekly	ref	-	0.000
	Less than weekly	0.3	-0.7 – 1.3	0.547
	Never	-2.0	-3.1 – -0.8	0.001
LL moderate activity	At least weekly	ref	-	0.003
	Less than weekly	1.4	-0.1 – 2.8	0.061
	Never	-1.8	-3.4 – -0.2	0.027
LL puzzles	At least weekly	3.0	1.7 – 4.2	0.000
	Less than weekly	0.8	-1.4 – 3.0	0.469
	Never	ref	-	0.000

7.6.3 Discussion

The main finding was that later life education was associated with better overall cognition (covering all cognitive domains in Table 7.2) over and above education in young adulthood. Although there was no direct association, education in midlife also contributed to better cognition through a greater likelihood of completing later life education. It was essential to adjust for age in the model and after adjusting for cognitive reserve as well as demographic and health variables the direct associations between young adulthood education and later life education with cognition were still important.

This work is able to add to the literature as it provides a comprehensive analysis of lifelong education and overall cognition whilst also adjusting for demographic, health and cognitive reserve variables. Unlike many earlier studies of lifelong education CamCAN is population based

and inverse probability weighting ensured the results were representative. The ACE-R is a comprehensive measure for global cognition and is commonly used in clinical practice. There were a number of limitations to this work. The cross-sectional design is the most important limitation, although a path analysis was used to infer causation, reverse causation cannot be ruled out. Cross-sectional data on different life stages relied on the participant's memory of young adulthood, midlife and later life and also meant that previous cognition could not be adjusted for in the model. Different levels of qualifications were included in the self-completion questionnaire for midlife and later life but due to low numbers had to be grouped with no qualifications. For instance in later life only four completed GCSE qualification, one completed A-level qualifications and 15 completed university level education. The ACE-R is amenable to being split into sub-sections for different cognitive domains, here it was only considered as overall cognition, to ensure false positive models from over fitting. For the models to converge it had to be assumed that self-completion questionnaires that were returned with incomplete sections were because the participant had not taken part in those activities, although such assumptions cannot be made in complete confidence. Even with these assumptions, there was still not enough variation within the data to complete mediation analysis with a latent variable to investigate the direct association between education and cognition in comparison to the indirect association of education with cognition through cognitive reserve. This also limited the number of covariates that could be added to the latent model. Due to the inverse probability weighting an overall measure of model fit could not be calculated. The use of Wald tests as a substitute for modification indices provided some confirmation of variables that should remain in the model, however the possibility of over fitting means these results should be interpreted with caution.

In line with the published research into lifelong education and cognition [319-322], this analysis found an association between later life education and better cognition. However, methodological differences in study design, educational and cognition measurements prohibited direct comparison with other studies. Study design of CamCAN and education measurement was most similar to the British 1946 birth cohort study. Whilst CamCAN is cross-sectional, the British 1946 birth cohort study is longitudinal although the analysis did not take into account longitudinal design [319]. Other differences include all those in the British 1946 birth cohort study were 53 at measurement of cognition but in CamCAN the age range included for this analysis was anyone aged 55 years and above. One other study previously tested overall cognition for working memory executive function, language processing cognitive domains together [322], the overall

cognition measurement used here (ACE-R) covered these three cognitive domains and in addition included episodic memory. Together these findings provide further support for the notion that continuing education beyond young adulthood may have implications for the reduction of dementia risk.

As previously mentioned in the background section of this chapter, randomised controlled trials targeting multiple domains of cognitive reserve have had mixed results. The only trial that showed an improvement in cognition ran a high intensity intervention combining cognitive training, nutritional advice and physical activity (FINGER [314]). The Tasmanian Healthy Brain Project (THBP) for ethical reasons could not randomise participants to a year in university level education. However, before further randomised controlled trials with education as either the sole intervention or as part of a multi-domain trial can be run further research would be beneficial. There were not the numbers needed in CamCAN to analyse each level of education at each time point in life but results from both CamCAN and the British 1946 birth cohort showed promising results that different levels of education still improved cognition. More research into 'dose' response to education is needed as intervention may not need to be as intense as university level education. Style of learning, whether learning remotely or in classes, part time or full time has also not been researched previously or controlled for, which could have a large impact on the efficacy of an education intervention. The first part of this chapter conducted a systematic review on lifelong education and dementia that resulted in no literature on the subject and the search had to be broadened to include cognition, even within that search evidence was limited. Research into lifelong education with dementia as the outcome rather than cognition would also be beneficial.

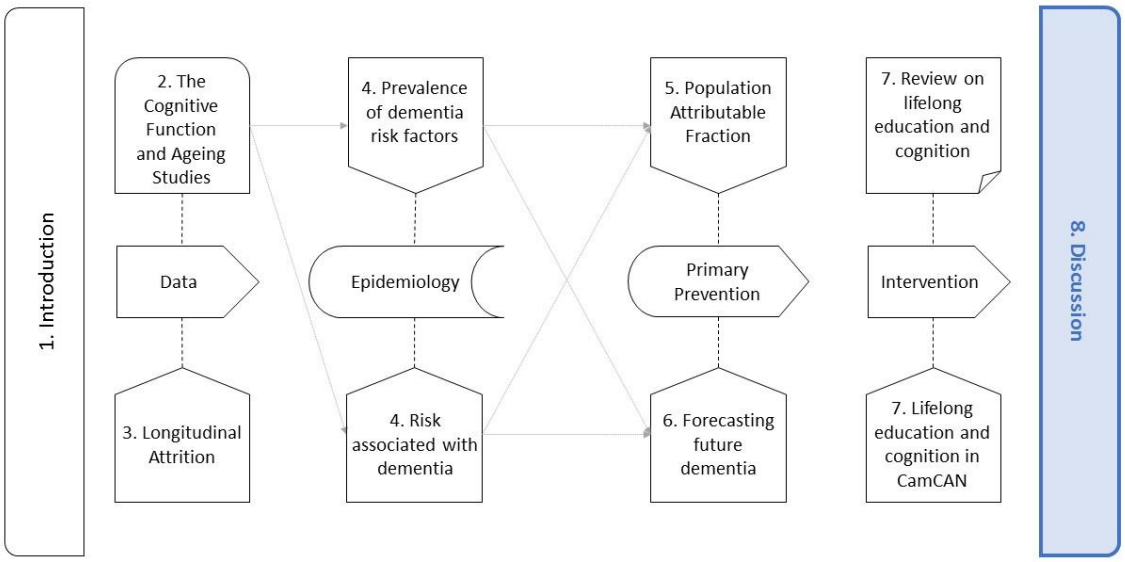
7.7 Chapter Conclusions

Continuing education in midlife or later life could potentially be used as an intervention to improve cognition and therefore prevent dementia. Lifelong education could be a good candidate for randomised controlled trials to prevent dementia either alone or as a component of a multi-domain trial but further research is needed before this is considered.

Chapter 8: Discussion

8.1 Chapter overview

This chapter discusses the thesis as a whole. A summary of the main findings, the strengths and limitations of the collective work, interpretations and implications of the main findings and conclusions are provided.



8.2 Main findings

8.2.1 Risk associated with dementia and prevalence of risk factors

Risk associated with dementia has remained relatively stable over time (Chapter 4). Low education, stroke, Parkinson's disease, poor self-perceived health and loneliness have remained robust targets for dementia prevention over time. Living in care settings and severe functional

impairment were associated with increased risk of dementia in both studies but are not considered modifiable for the prevention of dementia. In addition, unskilled occupation, widowhood, living in semi-dependent housing, current smoking and infrequent alcohol consumption were associated with increased risk of dementia in CFAS II but not in CFAS I. Physical inactivity was also associated with increased risk of dementia in CFAS II but was not included in CFAS I interviews. These findings support evidence from other research on occupation level, smoking and physical inactivity, all of which could be modifiable for dementia prevention. However, evidence on the association between alcohol and dementia is mixed and there is not enough evidence to suggest that increasing alcohol consumption would protect against dementia. Visual impairment and transient ischaemic attack were associated with increased risk of dementia in CFAS I but not in CFAS II.

The prevalence of many health and lifestyle factors have changed over time (Chapter 4). The proportion of people going into higher education is greater now than before but this has not resulted in an increase in the proportion of people going into highly skilled occupations. In fact studying occupation level by education level showed that only those with more than compulsory schooling went into highly skilled occupations, even though compulsory school leaving age increased between CFAS I and CFAS II. Prevalence of stroke was similar in both studies whereas transient ischaemic attack prevalence decreased between CFAS I and CFAS II. Prevalence of hypertension and diabetes increased over time but unlike other investigations neither were associated with dementia in either study.

8.2.2 PAF associated with dementia

Changes in prevalence and risk of dementia resulted in changes to the PAF associated with dementia over time (Chapter 5). The risk factors considered for the total combined PAF included education, occupation, transient ischaemic attack, stroke, fits/epilepsy, headaches, Parkinson's disease, anaemia, visual impairment, self-perceived health, loneliness, smoking and alcohol consumption. The total combined PAF was associated with a larger proportion of incident dementia cases in CFAS II than in CFAS I, stemming from an increase in the proportion of incident dementia cases associated with the proximal model (self-perceived health, loneliness, smoking and alcohol intake).

PAF associated with dementia from individual risk factors has also changed over time. The proportion of incident dementia cases associated with low education has decreased over time due to the decrease in proportion of people with low education. The unskilled occupation PAF associated with dementia, however, has increased due to unskilled occupation being associated with increased risk of dementia in CFAS II but not in CFAS I. The proportion of incident dementia cases associated with individual health conditions has remained stable over time, apart from a large decrease in the visual impairment PAF. PAF from individual proximal risk factors also remained stable over time, the exception being for alcohol intake, although this was measured differently in both studies.

8.2.3 Dementia Forecasting

A combination of forecasting methodology was used to take into account demographic and dementia risk factor trends, risk associated with dementia and the overlap between risk factors. Dementia forecasts taking into account education, midlife obesity, midlife hypertension, stroke and smoking estimated fewer future dementia cases in comparison to a simple extrapolation model. However, dementia prevalence is still expected to rise in the future. Higher education and reduction of midlife obesity and stroke prevalence could help to attenuate expected dementia cases but the increase in the ageing population will continue to impact on the absolute numbers for decades to come.

8.2.4 Lifelong education and cognition

The systematic review showed that there has been little research conducted on the association between continued education in later life and cognition. However, each study conducted previously showed that lifelong education was associated with better or improved cognition. The majority of the studies were not based on population representative samples. The one study with population representative data was unable to look at cognition past the age of 53 years.

To address these limitations, structural equation modelling was conducted using the CamCAN study, a population based study. In addition to young adulthood education, later life education was associated with better cognition. This was the case even after adjusting for cognitive reserve. Midlife education contributed to better cognition indirectly through increased likelihood of going on to later life education.

8.3 Critique of methods

8.3.1 Strengths

Both CFAS I and CFAS II are large multi-centre population based longitudinal studies, designed primarily to investigate dementia. Identical sampling design allows accurate temporal comparisons that are representative of the older population at each time point. Those living in care settings, an important population when studying dementia, are often excluded from surveys but were included in CFAS I and CFAS II.

Study dementia diagnosis in CFAS I and CFAS II, ascertained using the GMS AGECAT algorithm, remained the same between studies unlike changing clinical diagnosis over the last two decades. Any changes in risk estimates associated with dementia can therefore be seen as true changes in risk rather than changes in diagnostic criteria.

CamCAN is also a large population based study, designed to look at healthy brain ageing. All three studies, CFAS I, CFAS II and CamCAN were all population based, therefore offering unique advantages for studying the associations between risk factors and dementia in representative populations. This information can be utilised to improve cognition on an individual and population level.

8.3.2 Limitations

8.3.2.1 Study design

Although CFAS I and CFAS II were designed to investigate cognition and dementia in the population, study dementia diagnosis in CFAS I was conducted on a 20% subsample of the baseline participants. As study dementia diagnosis was missing for 80% of baseline participants by study design, 100 dementia imputed datasets were created for CFAS I in order to estimate temporal changes in prevalence and incidence of dementia between the two studies. Although this was not necessary for CFAS II, equivalent methods were used for analysis and 100 dementia imputed datasets were created for CFAS II. Dementia prevalence and incidence from these imputations has been reported [6, 7] and the same imputed datasets were used here for risk estimates that corresponded with the prevalence and incidence estimates. Imputation was used to account for item non-response within dementia risk factors. As imputation including the outcome as well as predictors is preferable [168], dementia was included in the risk factor imputations as a non-missing variable. Excluding factors from the imputation model could result in incorrectly weakened associations, complete-case analysis is recommended to compare with imputed analysis [171]. The complete-case analysis estimates were all within bounds of the 100 imputed datasets analysis estimates for CFAS II. Although for CFAS I some associations were stronger in the complete case analysis than in the 100 imputed datasets analysis, this was more likely due to low numbers rather than estimates being falsely weakened (Chapter 4). Dementia already being imputed prior to the risk factors could introduce bias as the risk factor imputations could be influenced by extreme dementia prevalence and incidence estimates. A sensitivity analysis reduced concerns on this issue, results from 20 imputations where dementia and risk factors were imputed together aligned closely to results where dementia was imputed prior to risk factors (Chapter 4).

The CamCAN study at baseline home interview was population representative. The majority of the lifelong education and cognitive reserve variables were derived from questions in the self-completion questionnaire. Those who returned their self-completion questionnaire had different characteristics to those who did not return their self-completion questionnaires but who did complete the home interview. Inverse probability weighting was used to account for these

differences and also initial non-response. It is likely that Cambridge may not be representative of the UK and therefore the results may not generalise to the UK population. However, whilst the actual numbers represented within the different education groups may not represent the population as a whole, each component of education was represented so relative measures should be robust.

8.3.2.2 Analysis

Limitations to individual analyses are provided within each chapter. These limitations apply to the thesis as a whole. Mortality was not accounted for in any of the analyses included in this thesis. For the analyses conducted using CFAS I and CFAS II those who died between baseline and two-year follow-up interview were excluded from the analysis. Models can be developed to account for mortality and potentially unmeasured dementia before death however the scope of the thesis was on the impact of health and lifestyle factors in those who remain alive to be influenced by it. Given that many of these risk factors are associated with both dementia (Chapter 4) and death (Chapter 3), exclusion of mortality may result in risk being under estimated. For example, risk of dementia could be underestimated if the risk factor (eg. smoking) caused death before the development of dementia. If dementia risk estimates were attenuated by the exclusion of mortality as a competing risk this would impact both the decision to include individual risk factors in the PAF and forecasting analyses and the PAF and forecasting estimates themselves. A stronger risk association would result in a larger proportion of incident dementia cases being associated with an individual risk factor. Life expectancy for those with (for instance smoking) and without risk factors in the generations studied has increased over time. Including mortality in the forecasts would likely result in increases to expected future dementia cases due to increased risk of dementia from older age, as discussed in Chapter 6. Including higher risk estimates would likely increase expected future dementia cases further.

Many hypotheses have been tested simultaneously during the course of this work without adjustment for multiple testing. Conducting multiple tests increases the probability of an observed association being due to chance. All risk factors investigated were specified a-priori based on previous literature and work from MRC CFAS. Further analysis was only conducted when in doubt of an association, not in an attempt to find an association.

8.4 Interpretation of findings

The main findings from this thesis concern the prevention and intervention of dementia. At the end of each chapter a discussion of the main findings has been provided. Here, the focus is on the interpretation of these findings as a whole and implications for future research.

8.4.1 Prevention

The analysis comparing dementia risk estimates in CFAS I and CFAS II is one of few studies that reports similarities and differences of a wide range of risk factors and their association with dementia [23, 49]. Each analysis has identified differences in risk associated with dementia over time for a few of the risk factors studied. Although there is disagreement on which risks are changing over time, there is agreement that the majority of dementia risks have remained stable. Risk factors such as low education level, unskilled occupation level, stroke, loneliness and physical inactivity are important for dementia prevention. Prevalence of individual dementia risk factors was also studied in CFAS I and CFAS II and many have changed greatly over time. Temporal changes in dementia prevalence and incidence are therefore more likely to have occurred due to changes in prevalence of dementia risk factors rather than risk associated with dementia itself. For instance current smoking prevalence has decreased over time and more people are going into further education now than before.

PAF analysis in CFAS I and CFAS II provided further insight into the impact of dementia risk factor prevalence trends on incident dementia. Changes to dementia PAFs over time have mainly been from changes in dementia risk factor prevalence. For instance the percentage of incident dementia cases associated with low education level has decreased over time because there are now more people going into further education than before. Using the PAF to measure percentage of incident dementia cases associated with individual and grouped risk factors over time is a helpful metric to see where prevention would be most advantageous at population level.

Although PAF of dementia associated with education decreased between CFAS I and CFAS II, based on evidence here and from other studies, low education level should remain a focus of dementia prevention [38, 47, 49]. Given the increase in percentage of incident dementia cases associated with proximal risk factors, a continued focus on loneliness [47], physical inactivity [38, 47] and smoking [38, 47] is also recommended. The fully combined PAF measures the percentage of incident dementia cases associated with all the risk factors considered in this analysis and a high percentage of incident dementia cases were not associated with any of the risk factors considered. Instead, these incident dementia cases could be associated with risk factors that were included in this analysis but considered non-modifiable or were not associated with any of the risk factors considered in this analysis but associated with other excluded risk factors. Another reason could be that these incident dementia cases were not associated with any risk factors, measured or otherwise.

Looking at dementia PAFs over time can give further insight into how changes in dementia risk factor prevalence contribute to identified incident dementia cases, but does not give information on whether more or less incident dementia cases occurred due to these changes in risk factor prevalence. Forecasting dementia prevalence showed the extent to which trends in prevalence of dementia risk factors could potentially amplify or attenuate future numbers of people with dementia. Increasing trends in prevalence of midlife obesity and stroke enlarged estimates of future number of people with dementia. Increases in higher education and decreasing trends in prevalence of hypertension and smoking contributed to the attenuation of future dementia cases. Declining prevalence of midlife obesity or stroke could also lead to reductions in future dementia numbers. Other dementia forecasts that include mortality suggest that prevention of dementia risk factors could increase dementia prevalence in the future as more individuals will live to older ages which is associated with increased risk of dementia [150, 263].

8.4.2 Recommendations for dementia prevention

Reductions of 5-10% in risk factor prevalence could be achieved through public health interventions. Many public health measures have already been introduced to prevent cardiovascular diseases such as stroke, hypertension and obesity. “Change4Life” promotes healthy lifestyle choices [343] and smoking cessation advice is available on the NHS [344].

Smoking in enclosed public spaces was prohibited, reducing exposure to second hand smoke as well as the prevalence of smoking [181]. Large taxes on cigarettes and health warnings on their containers have been introduced which increase awareness of the dangers of smoking and discourage buying large quantities of cigarettes. Targeting automatic decision making [345] could improve uptake of public health interventions. The UK government previously invested in a 'nudge' initiative, formally known as the Behavioural Insights Team which in conjunction with Public Health England have produced a report with suggestions to reduce smoking and obesity [346]. An example for obesity prevention is that research has shown snack consumption increases if food advertisements are shown during TV programmes [347]. Recently, unhealthy food advertisements were banned during children's programmes [348]. There has been both praise and criticism of the use of 'nudge' initiatives for tackling obesity [349] but many have not been running long enough to judge their effectiveness.

8.4.3 Intervention

The literature review on lifelong education and cognition provided positive indications of the benefits of continuing education after young adulthood on cognition [319-322]. Previous analysis on a population based representative sample only had information on lifelong education and cognition up to the age of 53 years [319]. The CamCAN analysis was able to add to this evidence by providing results on a population based sample aged 55 years or over. Fully adjusted results from CamCAN showed that continuing education in later life (aged 65 years or more) was associated with better cognition. Midlife education was indirectly associated with higher cognitive test scores by increasing the likelihood of an individual continuing to later life education. Before adjusting for age, midlife education had been directly associated with better cognition and later life education was not associated with cognition. This means that in CamCAN the association between midlife education and better cognition was mainly due to natural cognitive decline with age. Longitudinal research using population based studies would help to determine when during the lifespan education intervention would be most appropriate for preventing cognitive impairment or dementia. Before further trials on education as an intervention for cognitive impairment or dementia are conducted further research is needed.

8.5 Future work

Other studies suggest an association between risk factors identified in midlife rather than later life and dementia [36]. Further research is needed into whether risk of dementia from midlife risk factors has changed over time. Given that a proportion of incident dementia cases were not associated with any of the risk factors considered in the PAF analysis, analysis on dementia PAF for midlife risk factors could help to identify the most important risk factors to target. Analysing PAF for dementia from midlife risk factors could also help to determine whether it is more important to prevent proximal or midlife risk factors.

As mentioned previously, forecasting dementia for the UK using micro-simulation would be the most accurate method to estimate future dementia prevalence. Micro-simulation is able to take into account everything from these forecasts: ageing population, demographic trends, association between risk factors and dementia, prevalence trends of dementia risk factors and overlap between dementia risk factors. In addition micro-simulations can also take into account mortality, including mortality trends over time and mortality differences between those with and without dementia or with and without risk factors. A micro-simulation model from the USA suggests that reducing the prevalence of dementia risk factors will contribute to an increase in dementia cases in the future compared to expectations under current trends [263]. This is in opposition to findings from this thesis suggesting that reductions in dementia risk factors will result in reductions in future dementia cases compared to current expectations. Including mortality is likely to have the same impact to UK dementia forecasts as in general those without risk factors will live longer than those with risk factors and older age is one of the largest risk factors for dementia [150]. Current risk factor trends differ in the UK to the US and therefore micro-simulation models of dementia in the UK with scenarios for risk factor reductions are required to accurately estimate future dementia cases. Although micro-simulation models are currently the best method for forecasting dementia accurately, they do not come without limitations. Micro-simulation models have a long set up period and the amount of information needed is vast. On top of information used in the forecasts here, mortality differences between those with and without risk factors and with and without dementia would be needed. As the number of risk factors included in the model increases, information on the relationships between risk factors and dementia will grow and become more complex. The size of the original dataset that the micro-

simulation model is based on needs to be large to allow the modelling of each component simultaneously. Without a large enough sample the model could potentially be prone to overfitting, driven by small numbers in risk factor and dementia subgroups.

As previously stated there are areas of research for lifelong education and cognition that have not yet been covered. Intervention trials targeting other areas of cognitive reserve have had mixed results [312-314], with the most successful also being the most intense intervention [314]. Before further trials on education as an intervention for cognitive impairment or dementia, information on intensity of intervention is required. University level education is currently being implemented as an intervention [320, 322] but results from CamCAN and the 1946 British birth cohort [319] suggest lower levels of education in later life could still be beneficial. If lower than university level education can be used as an intervention this could be accessed by individuals that have not reached the level of education required to enrol in university and could also potentially be less costly. Learning style, whether part-time/full-time, remotely or in a class could have a large impact on the efficacy of an education intervention. If further research shows that remote learning is just as effective at preventing cognitive impairment or dementia as learning in a classroom with a structured environment, this could be easier to implement. Longitudinal analysis has shown that later life education is associated with improved cognition [320, 322]. Longitudinal analysis using population based studies could highlight any long-term advantages to continuing education. Lastly, a lifelong education and dementia review resulted in no literature on the subject and therefore is a research topic with opportunities for development.

8.6 Conclusion

In summary, this work provides supporting evidence that dementia risk has mainly remained stable over time. Changes in dementia prevalence and incidence are more likely due to trends in prevalence of dementia risk factors. Further research into risk reduction and future dementia is recommended before implementing prevention strategies. Continuing with education in later life is associated with better cognition. Research using longitudinal population based studies with identical measures of cognition over time would show whether completing education in later life

is associated with improved cognition over time. Prior to further intervention studies on lifelong education either individually or as part of a multi-dimensional intervention trial, further research into education level and learning style is needed to construct the most efficient intervention.

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Appendices

A1: Questions from CFAS I and CFAS II used to create variables

Marital status (Q11 in CFAS I, Q4 in CFAS II) and place of residence (ITEM 12 in CFAS I, Q6 in CFAS II):

Q11 Are you married, single, widowed or divorced? (If NO are you separated or do you have a partner?) 1. Married 2. Cohabiting 3. Single 4. Widowed 5. Divorced/Separated	Q11 For multiple marriages code current status.
ITEM 12 Establish type of accommodation. 1. House/Flat/Granny flat 2. Warden Controlled flat 3. Council Residential home 4. Private Residential home 5. Private Nursing Home 6. Long stay hospital 7. Not established IF THE ANSWER TO Q12 IS 3,4,5 OR 6 SKIP TO Q15	ITEM 12 Bungalow - rate as house. Rate 3 for Part III Accommodation. If the respondent is in an Elderly Mentally Infirm Unit within an institution rate as for the institution.

Education (Q16 in CFAS I, Q40 in CFAS II):

Q16 How many years did you spend in full-time education? Answer in years nn 77 Don't know	Q16 Most people will have had either 8 or 9 years at school, with a starting age of 5 or 6 and a leaving age of 13 or 14. Include years in full-time higher education.

Social class (Q19 in CFAS I, Q45 in CFAS II):

Q19 What has been your main occupation for most of your working life? Textual answer	Q19 Complete for the occupation that was held for the longest period, even if it is not the most recent. Give a detailed job title.

Angina (Q41 in CFAS I, Q396 in CFAS II):

Q41 Have you ever suffered with angina. 0. No 1. Yes 8. No answer 9. Not asked	Q41 Rate here if the subject has been diagnosed by a doctor as suffering with angina. If answer is No enter the skip section.

Peripheral vascular disease (Q51-60 in CFAS I for Rose scale, Q397 in CFAS II):

Q51 Have you ever suffered from intermittent claudication? 0. No 1. Yes 8. No answer 9. Not asked	Q51 Rate here if a doctor has made a diagnosis for intermittent claudication. If subject's answer is No, or they don't know, go into the skip section
IF YES SKIP TO Q61	

Q52 Do you get pain in either leg on walking? 0. No 1. Yes 2. Chair/Bedfast 8. No answer 9. Not asked	Q52-Q60 These 9 questions are designed to elicit information for a diagnosis of intermittent claudication in the absence of the subject's knowledge. Contra indications to the diagnosis cause a skip to the next section.
IF NO OR CHAIR/BEDFAST SKIP TO Q61	
Q53 Does this pain ever begin when you are standing still or sitting? 0. No 1. Yes 8. No answer 9. Not asked	
IF YES SKIP TO Q61	
Q54 In what part of your leg do you feel it? 0. Not in calf or calves 1. In calf or calves 8. No answer 9. Not asked	
IF CALVES NOT MENTIONED, ASK: Anywhere else? IF NOT IN CALVES SKIP TO Q61	
Q55 Do you get it if you walk uphill or hurry? 0. No 1. Yes	

2. Never hurries or walks uphill 8. No answer 9. Not asked	
IF NO SKIP TO Q61	
Q56 Do you get it if you walk at an ordinary pace on the level? 0. No 1. Yes 2. Never walks 8. No answer 9. Not asked	
IF YES SKIP TO Q61	
Q58 What do you do if you get it when you are walking? 1. Stop or slow down 2. Carry on 8. No answer 9. Not asked	
Q59 What happens to it if you stand still? 0. Not relieved 1. Relieved 8. No answer 9. Not asked	
Q60 How soon? 1. 10 minutes or less 2. More than 10 minutes	

8. No answer 9. Not asked	

Heart attack (Q61 in CFAS I, Q423 in CFAS II):

Q61 Have you ever suffered from a heart attack? 0. No 1. Yes 8. No answer 9. Not asked	

High blood pressure (Q66 in CFAS I, Q399 in CFAS II):

Q66 Have you ever been told that you have high blood pressure? 0. No 1. Yes, by GP 2. Yes, by other 8. No answer 9. Not asked	Q66 Exclude high blood pressure in pregnancy.

Stroke (Q69-70 in CFAS I, Q418 and Q420 in CFAS II):

Q69 Have you ever had a stroke that required medical attention? 0. No 1. Yes 8. No answer 9. Not asked	Q69 Record only episodes that lasted for 48 hours or longer with partial paralysis in left or right arm and/or leg, blindness in eye/s, or speech disturbance. Ensure that respondent doesn't mean a heart attack. Rate No if the respondent does not know or cannot remember. Paralysis on the right hand side of the face may be associated with speech difficulty.
IF NO SKIP TO Q74	
Q70 How many have you had? Number of strokes nn 77 Don't know 88 No answer 99 Not asked	

Diabetes (Q79 in CFAS I, Q409 in CFAS II):

Q79 Are you currently being treated for your diabetes? (If YES what sort of treatment?) 0. No 1. Yes, dietary control only 2. Yes, injections 3. Yes, tablets 4. Yes, both 8. No answer 9. Not asked	

Fits/epilepsy (Q80 in CFAS I, Q427 in CFAS II):

Q80 Have you ever had fits or epilepsy? 0. No 1. Only 1 known fit 2. More than 1 fit 8. No answer 9. Not asked	

Head injury (Q81-82 in CFAS I, Q429-430 in CFAS II):

Q81 Have you ever had a serious head injury and been unconscious after it? (Have you ever been knocked out?) 0. No 1. Yes 8. No answer 9. Not asked	
IF NO SKIP TO Q85	
Q82 How many times? Number of times nn 77 Don't know 88 No answer 99 Not asked	Q82 If number is greater than 3, answer Q83 and Q84 for the longest three incidents.

General anaesthetic (Q86-87 in CFAS I, Q434-435 in CFAS II):

Q86 Have you ever had a general anaesthetic? (If NO: have you ever had a major operation?) 0. No 1. Yes 8. No answer 9. Not asked	
IF NO SKIP TO Q88	
Q87 How many times? Number of times	Q87 Rate 77 for Don't know; 88 for No answer; 99 for Not asked.

Self-reported depression (Q88 in CFAS I, Q126 in CFAS II):

Q88 Have you ever consulted a doctor about emotional problems, or problems with your nerves? Perhaps if you were depressed or anxious, or found that you couldn't enjoy yourself? 0. No 1. Yes, sounds like depression 2. Yes, sounds like anxiety 3. Yes, other 8. No answer 9. Not asked	Q88 Depression: Feeling low in mood, no sleep, loss of weight, not able to get things done. Anxiety: Feelings of impending panic.

Headaches (Q94 in CFAS I, Q442 in CFAS II):

Q94 Do you suffer from regular headaches? 0. No 1. Yes, non specific 2. Yes, migraine 8. No answer 9. Not asked	

Hearing difficulties (Q95 in CFAS I, Q450 in CFAS II):

Q95 Do you suffer from hearing problems which interfere with day-to-day living? 0. No 1. Yes 8. No answer 9. Not asked	Q95 If hearing is not problematic because the subject uses an aid then rate 0.

Visual impairment (Q96 in CFAS I, Q459 in CFAS II):

Q96 Do you suffer from poor eyesight which interferes with day-to-day living? 0. No 1. Yes 8. No answer 9. Not asked	Q96 To count as poor eyesight must interfere even when wearing glasses. If subject wears glasses all the time or in certain conditions but otherwise reports no problems, rate 0.

Breathing difficulties (Q97 and Q99 in CFAS I, Q436 and Q437 in CFAS II):

Q97 Have you ever suffered from asthma? 0. No 1. Yes, childhood only 2. Yes 8. No answer 9. Not asked	
Q99 Have you ever suffered with chronic bronchitis? 0. No 1. Yes 8. No answer 9. Not asked	

Arthritis (Q98 in CFAS I, Q439 in CFAS II):

Q98 Have you ever suffered from arthritis? 0. No 1. Yes 8. No answer 9. Not asked	Q98 Rate for arthritis in any part of the body. Include persistent joint pain.

Thyroid problems (Q100 in CFAS I, Q447 in CFAS II):

Q100 Have you ever suffered from thyroid problems? 0. No 1. Underactive current 2. Overactive current 3. Other/non-specific current 4. Underactive past 5. Overactive past 6. Other/non specific past 8. No answer 9. Not asked	

Peptic ulcers (Q101 in CFAS I, Q443 in CFAS II):

Q101 Have you ever suffered from peptic ulcers? 0. No 1. Yes 8. No answer 9. Not asked	Q101 Rate for both gastric and duodenal ulcers.

Anaemia (Q102 in CFAS I, Q444 in CFAS II):

Q102 Have you ever suffered with pernicious anaemia? 0. No 1. Yes 8. No answer 9. Not asked	

Meningitis (Q103 in CFAS I, Q478 in CFAS II):

Q103 Have you ever suffered from meningitis or encephalitis (brain fever)? 0. No 1. Yes, meningitis 2. Yes, encephalitis 3. Yes, non specific 8. No answer 9. Not asked	

Shingles (Q104 in CFAS I, Q479 in CFAS II):

Q104 Have you ever suffered from shingles? (If YES, Where?) (If HEAD NOT MENTIONED: Anywhere else?) 0. No 1. Yes, in the body 2. Yes, in the head 8. No answer 9. Not asked	Q104 The location of shingles is important here. Shingles in the trunk is less significant than shingles in the head. Rate in the head for shingles on the face, in the eyes, in the ears or on the scalp.

Parkinson's disease (Q105 in CFAS I, Q412 in CFAS II):

Q105 Have you ever been diagnosed as having Parkinson's disease? 0. No 1. Yes 8. No answer 9. Not asked	

Transient ischaemic attack (Q74-76 in CFAS I, Q445-446 in CFAS II):

Q74 Have you ever experienced sudden problems with your speech WHICH GOT BETTER AFTER A DAY? 0. No 1. Yes 8. No answer 9. Not asked	Q74 Include unclear speech, not being able to pronounce words that are definitely known and not forming the correct sound. Episodes to last less than 24 hours.
Q75 Have you ever experienced problems with your sight WHICH GOT BETTER AFTER A DAY? 0. No 1. Yes 8. No answer 9. Not asked	Q75 Include double vision, no vision, black in front of one/both eyes or something in vision (such as a beam, line or spot). Episodes to last less than 24 hours.
Q76 Have you ever experienced a sudden weakness in an arm or leg WHICH GOT BETTER AFTER A DAY? 0. No 1. Yes 8. No answer 9. Not asked	

Self-perceived health (Q40 in CFAS I, Q374 in CFAS II:

Q40 Would you say that for someone of your age, your own health in general is: 0. Excellent 1. Good 2. Fair 3. Poor 8. Don't know 9. Not asked	

Functional impairment (Q122, 125-127, 130, 149 in CFAS I, Q533, 537-539, 542, 559 in CFAS II):

Q122 Are you able to wash all over or bath? (If YES: Do you have difficulty?) 0. No, needs help 1. Yes, some difficulty 2. Yes, no difficulty 7. Don't know 8. No answer 9. Not asked	People with mental frailties who cannot undertake activities because of their mental frailty should be coded as needing help.
Q125 Are you able to do heavy housework? (If YES: Do you have difficulty?) 0. No, needs help 1. Yes, some difficulty 2. Yes, no difficulty 7. Don't know 8. No answer 9. Not asked	Q125 Heavy Housework – for example, washing floors.

Q126 Are you able to shop and carry heavy bags? (If YES: Do you have difficulty? 0. No, needs help 1. Yes, some difficulty 2. Yes, no difficulty 7. Don't know 8. No answer 9. Not asked	
Q127 Are you able to prepare and cook a hot meal? (If YES: Do you have difficulty?) 0. No, needs help 1. Yes, some difficulty 2. Yes, no difficulty 7. Don't know 8. No answer 9. Not asked	Q127 If the subject claims they never have to cook a hot meal because this is always done for them, ask them to make a judgement as to whether they could if they had to.
Q130 Are you able to put on your shoes and socks or stockings? (If YES: do you have difficulty?) 0. (No), needs help 1. (Yes), some difficulty 2. (Yes), no difficulty 7. Don't know 8. No answer 9. Not asked	
ITEM 149 Establish degree of mobility of subject. 1. Usually ambulant non-housebound	I149 Where subject's degree of mobility is obvious you may code from observation or from information already obtained. However check that the observed state is permanent and not temporary i.e. the subject is not expected to

2. Usually ambulant housebound 3. Chairfast permanently 4. Bedfast permanently 7. Unable to establish mobility	improve markedly in the short term. If in doubt over-estimate degree of disability and notify. Rate 1 - For people who are usually able to get out without assistance. Rate 2 - For people who can get about on the level inside but who never go out of the house or garden without assistance. Rate 3 - For people who spend all their time confined to a chair or who need help to transfer from the chair to the toilet or bed. Use this rating for a wheelchair user even if they can get out of the house. Rate 4 - For people who spend all their time confined to bed.

Loneliness (Q in A0 rather than S0 in CFAS I, Q212 in CFAS II):

Q212 Do you feel lonely? 0. No 1. Infrequently 2. Frequently/Persistently 8. No answer 9. Not asked	Q212 Here R simply admits to feeling lonely. The reasons for feeling lonely are not explored and the feeling itself is simply rated. It should fulfil the criteria of being unpleasant and not under voluntary control, but it is not necessarily out of proportion to the circumstances as these in any case would be difficult to judge.

Friendships (QN12 in CFAS I, Q76 in CFAS II):

QN12 Do you have friends in this community? (If Yes how often do you have a chat or do something with one of your friends?) 0. No friends/Never 1. Daily 2. 2-3 times a week 3. At least weekly 4. At least monthly 5. Less often 8. No answer 9. Not asked	Qn12 Rate 'face to face' rather than telephone calls.

Frequency of seeing relatives (QN9 in CFAS I, Q63 from CFAS II)

QN9 How often do you see any of your (children or other) relatives to speak to? 0. Never 1. Daily 2. 2-3 times a week 3. At least weekly 4. At least monthly 5. Less often 8. No answer 9. Not asked	QN9 Here you must rate cumulative contact – if the subject sees a different relative every day rate as 1 – daily contact.

Smoking (Q150, 152, 153 in CFAS I, Q500, 502, 503 in CFAS II):

Q150 Do you smoke? 0. No 1. Yes 8. No answer 9. Not asked	
IF NO SKIP Q152	
Q152 Have you ever smoked? 0. No 1. Yes 8. No answer 9. Not asked	
IF NO SKIP TO Q156	
Q153 How old were you when you stopped? Age in years nn	Q153 Record subject's age when they last stopped smoking. Enter 888 if no answer and 999 if not asked.

Alcohol intake in CFAS I (Q156):

Q156 Have you every taken an alcoholic drink of any kind? 0. No 1. Yes 8. No answer 9. Not asked	

Alcohol intake in CFAS II (Q508):

ALCOHOL INTAKE	
Q508 Thinking now about all kinds of drinks, how often have you had an alcoholic drink of any kind during the last 12 months. 1. Almost every day 2. Five or six days a week 3. Three or four days per week 4. Once or twice a week 5. Once or twice a month 6. Once every couple of months 7. Once or twice a year 8. Not at all in the last 12 months. 77 Don't know 88 No answer 99 Not asked	

A2: Combined PAF probability equation derivation

This chapter in the appendix gives the full derivation of Equation 5.2 from Equation 5.1 in the PAF chapter, following steps from Bruzzi et al. [240] and filling in gaps in between.

As in Bruzzi et al. let n be the total number of people in a population and y be the number of people with a disease (cases). y can be incident or prevalent cases. There are K covariates to be included in the PAF model (including but not limited to exposures and confounders) that are all categorical. The n individuals can be split into J distinct strata depending on their covariate pattern, where $J = 2^K$ if all covariates are binary. The probability that someone in stratum j is a case is given by $I_j = \frac{y_j}{n_j}$, where n is the number of people in stratum j and y is the number of cases in stratum j. Therefore the rate of disease in the total population is $I_T = \sum_j \frac{y_j}{n_j} = \frac{y}{n}$ and rate of disease in the lowest risk stratum ($j = 0$) is $I_0 = \frac{y_0}{n_0}$. In the unadjusted PAF I_T is compared to I_0 and therefore Equation 5.1:

$$PAF = \frac{Disease\ rate\ in\ total\ population - Disease\ rate\ in\ unexposed\ group}{Disease\ rate\ in\ total\ population}$$

can be written as the following from Bruzzi et al. [240]:

$$Unadjusted\ PAF = \frac{I_T - I_0}{I_T} \quad .$$

However, say the covariates can be split into two subsets, A representing risk factors and C representing confounders. Then the adjusted PAF estimates the PAF of risk factors in A whilst adjusting for the confounders in C. Therefore for the adjusted PAF Equation 5.1 can be written as:

$$Adjusted\ PAF = \frac{I_T - I_C}{I_T} = 1 - \frac{I_C}{I_T} \quad . \quad A3.1$$

from Bruzzi at al. [240]. If risk factors in A were eliminated but the levels of the confounders in C remained the same then I_C denotes the disease rate that would be observed. For every stratum j there will be another stratum j^* where risk factors in A are at lowest risk levels but levels for C are the same as in stratum j. The rate of disease in stratum $j^* = \frac{y_{j^*}}{n_{j^*}}$ where n_{j^*} is the number of

people in stratum j^* and $y_j{}^*$ is the number of cases in stratum j^*. Then $I_C = \sum_j I_j{}^*$ and substituting I_C and I_T into Equation A3.1 gives:

$$Adjusted\ PAF = 1 - \frac{\sum_j I_j{}^*}{y/n} \quad . \quad A3.2$$

This can be defined in terms of relative risk. First let R_j be the relative risk of being in stratum j in comparison to the stratum with the lowest risk ($j = 0$), $R_j = \frac{I_j}{I_0}$. Then the relative risk of being in stratum j in comparison to j^* is:

$$\widetilde{R_j} = \frac{R_j}{R_j{}^*} = \frac{I_j/I_0}{I_j{}^*/I_0} = \frac{I_j}{I_j{}^*}$$

and rearranging gives $I_j{}^* = \frac{I_j}{\widetilde{R_j}}$. Substituting $I_j{}^*$ into Equation A3.2 gives:

$$Adjusted\ PAF = 1 - \frac{\sum_j I_j/\widetilde{R_j}}{y/n}$$

Substituting in $I_j = \frac{y_j}{n_j}$ gives:

$$Adjusted\ PAF = 1 - \frac{\sum_j y_j/n_j\widetilde{R_j}}{y/n} = 1 - \frac{\frac{1}{n}\sum_j y_j/\widetilde{R_j}}{y/n} = 1 - \frac{\sum_j y_j/\widetilde{R_j}}{y} \quad , \quad A3.3$$

as in Bruzzi et al. [240]. This equation could also be used to denote unadjusted PAF because setting $j^* = 0$ gives $\widetilde{R_j} = \frac{R_j}{R_j{}^*} = \frac{R_j}{R_0} = \frac{R_j}{1} = R_j$, giving the same equation as the unadjusted PAF in Bruzzi et al. [240].

Equation A3.3 is equivalent to Equation 5.2 from Greenland and Drescher [234]:

$$PAF = 1 - \boldsymbol{p}'\boldsymbol{s} \quad ,$$

where vectors $\boldsymbol{p}$ and $\boldsymbol{s}$ both have J columns with elements

$$p_j = \Pr(\boldsymbol{x}_j | d_j = 1) \text{ and } s_j = \frac{\Pr(d_j=1\,|\boldsymbol{z}_j)}{\Pr(d_j=1|\boldsymbol{x}_j)}$$

respectively. d_j is a binary disease indicator (prevalent or incident depending on model) and $d_j = 1$ indicates occurrence of disease whereas $d_j = 0$ indicates no disease. Here p_j is equivalent to y_j/y and s_j is equivalent to $1/\widetilde{R_j}$.

The Greenland and Drescher equation could be used to denote both unadjusted and adjusted risk. If $\boldsymbol{z}_j$ was defined as the covariate pattern with lowest risk (equivalent to stratum $j = 0$ in Bruzzi et al.) then s_j would denote the inverse relative risk of having covariate pattern x_j in comparison to the lowest risk covariate pattern (equivalent to inverse R_j in Bruzzi et al.).

A common expression for adjusted individual PAF is $p\frac{\tilde{R}-1}{\tilde{R}}$ (from [235]) for a single binary risk factor when using an adjusted relative risk this produces an internally valid adjusted PAF where p is the proportion of disease cases with the exposure and R is the adjusted relative risk of disease from the exposure. In other words, if there was only one risk factor in A but still confounders in C then R is the relative risk of being in stratum j compared to j^*. With the same definitions as above where for every stratum j there will be another stratum j^* where risk factors in A (here only one binary risk factor) are at lowest risk levels but levels for C are the same as in stratum j. Equations A3.3 and 5.2 are the extension of this for the combined adjusted PAF summing over J strata when there are multiple rather than a single risk factor in A.

$$\sum_j p_j \frac{\widetilde{R_j} - 1}{\widetilde{R_j}} = \sum_j p_j \left(1 - \frac{1}{\widetilde{R_j}}\right) = \sum_j \left(p_j - \frac{p_j}{\widetilde{R_j}}\right)$$

but since $\sum_j p_j = \sum_j \frac{y_j}{y} = \frac{y}{y} = 1$,

$$\sum_j \left(p_j - \frac{p_j}{\widetilde{R_j}}\right) = 1 - \sum_j \frac{p_j}{\widetilde{R_j}} \ .$$

A3: Forecasting methodology examples

Example 1

This example goes through the methods for forecasting with a single risk factor, midlife obesity. As the method is repeated from 2011 to 2040, only 2011 is shown in this example. Before forecasting, the following estimates are needed.

Relative Risk (RR) of dementia for midlife obesity: 1.64

Appendix Table A3.1: Estimates needed for a midlife obesity single risk factor forecast in 2011, including dementia prevalence, obesity prevalence and population estimates by age and sex

Men	**2011 Dementia prevalence**	**2011 Midlife obesity prevalence**	**2011 Population estimates**
65-69	0.012	0.179	1491335
70-74	0.03	0.148	1158260
75-79	0.052	0.13	910082
80-84	0.106	0.107	620544
85-89	0.128	0.091	327153
90+	0.171	0.066	130127
Women			
65-69	0.018	0.211	1582085
70-74	0.025	0.19	1294725
75-79	0.062	0.179	1107015
80-84	0.095	0.154	886682
85-89	0.181	0.14	594414
90+	0.35	0.128	355764
		Total:	10458186

Step 1. Find dementia prevalence in risk factor reference category (no midlife obesity) using Equation 1 for an age and sex group. For instance, to calculate dementia prevalence in men aged 65-69 years with no midlife obesity:

$P_{tot} = 0.012$

$N_{tot} = 1491335$

$i = 2\ (no\ midlife\ obesity, obese\ in\ midlife)$

$N_{gp_1} = (1 - 0.179) \times 1491335 = 1224386.035$

$N_{gp_2} = 0.179 \times 1491335 = 266948.965$

$RR_{gp_2} = 1.64$

Giving:

$$P_{gp_1} = \frac{P_{tot} \times N_{tot}}{N_{gp_1} + (RR_{gp_2} \times N_{gp_2}) + \cdots + (RR_{gp_i} \times N_{gp_i})} = \frac{0.012 \times 1491335}{1224386.035 + (1.64 \times 266948.965)} = 0.010766581$$

Step 2. Find dementia prevalence in other risk factor categories using Equation 2 for an age and sex group, for this example, men aged 65-69 years who had midlife obesity.

$P_{gp_2} = RR_{gp_2} \times P_{gp_1} = 1.64 \times 0.010766581 = 0.017657192$

Step 3. Find number of people with dementia in risk factor reference category. In this example, the number of men aged 65-69 years with no midlife obesity but with dementia.

$N_{gp_1} \times P_{gp_1} = 1224386.035 \times 0.010766581 = 13182.45085$

Step 4. Find number of people with dementia in other risk factor categories. In this example, the number of men aged 65-69 years who had midlife obesity and also have dementia.

$N_{gp_2} \times P_{gp_2} = 266948.965 \times 0.017657192 = 4713.569149$

Step 5. Total number of people with dementia in an age and sex group.

$13182.45085 + 4713.569149 = 17896.02$

Step 6. Calculate new dementia prevalence – note that for 2011 risk factor prevalence has not changed yet, so neither has the dementia prevalence.

$17896.02 \div N_{tot} = 17896.02 \div 1491335 = 0.012$

Step 7. Repeat for each age and sex group to get total number of people with dementia in a year, here 2011.

Appendix Table A3.2: Completing method above for all age and sex groups gives the results in this table. The top row for men aged 65-69 years coincides with the results from above.

			Step 1	Step 2	Step 3	Step 4	Step 5	Step 6
Men	N_{gp_1}	N_{gp_2}	P_{gp_1}	P_{gp_2}	**No midlife obesity dementia cases**	**Midlife obesity dementia cases**	**Numbers with dementia**	**New dementia prevalence**
65-69	1224386.035	266948.965	0.010766581	0.017657192	13182.45085	4713.569149	17896.02	0.012
70-74	986837.52	171422.48	0.027404268	0.044942999	27043.55963	7704.240368	34747.8	0.03
75-79	791771.34	118310.66	0.048005908	0.07872969	38009.70244	9314.561563	47324.264	0.052
80-84	554145.792	66398.208	0.099206349	0.162698413	54974.78095	10802.88305	65777.664	0.106
85-89	297382.077	29770.923	0.120955549	0.1983671	35970.01234	5905.571663	41875.584	0.128
90+	121538.618	8588.382	0.164069696	0.269074302	19940.80411	2310.912888	22251.717	0.171
Women								
65-69	1248265.065	333819.935	0.015858472	0.026007894	19795.57652	8681.953483	28477.53	0.018
70-74	1048727.25	245997.75	0.022289586	0.036554922	23375.69655	8992.42845	32368.125	0.025
75-79	908859.315	198155.685	0.055627333	0.091228826	50557.41955	18077.51045	68634.93	0.062
80-84	750132.972	136549.028	0.086476842	0.141822022	64869.13081	19365.65919	84234.79	0.095
85-89	511196.04	83217.96	0.166116006	0.27243025	84917.84438	22671.08962	107588.934	0.181
90+	310226.208	45537.792	0.323498965	0.530538302	100357.8571	24159.54286	124517.4	0.35
						Overall:	675694.758	0.065

Points to note:

- Original Relative Risk (RR) for midlife obesity used as this is not adjusted for other risk factors
- In single risk factor forecasts there is an assumption that the prevalence of dementia in each category of the risk factor does not change as the other risk factors are not adjusted for

Example 2

This example goes through the method for a combined forecast. In this case, education is being added after midlife obesity.

Important to note: This example is for 2015 as changes in prevalence of risk factors occur after 2011.

Before forecasting the following estimates are needed. Adjusted relative risk of education, dementia prevalence in 2015 accounting for midlife obesity (results not given in main text, only in appendix), education prevalence in 2011, education prevalence in 2015 and population estimates for 2015.

Dementia prevalence 2015 accounting for midlife obesity is attained using the same method as in Example 1 but using 2015 population and midlife obesity prevalence estimates, and instead of the unadjusted RR of dementia for midlife obesity (1.64), the adjusted RR for midlife obesity (1.30).

Adjusted relative risk of dementia for education:

≤9 years 1.00

10-11 years 0.87

≥12 years 0.87

Appendix Table A3.3: Estimates needed for combined risk factor forecast for education after midlife obesity, including dementia prevalence at 2015 accounting for midlife obesity, education prevalence in 2011, education prevalence in 2015 and population estimates in 2015 by age and sex

Men	2015 Dementia prevalence accounting for midlife obesity	2011 ≤9 years education prevalence	2011 10 to 11 years education prevalence	2011 ≥12 years education prevalence	2015 ≤9 years education prevalence	2015 10 to 11 years education prevalence	2015 ≥12 years education prevalence	2015 Population estimates
65-69	0.012142017	0.0448	0.6632	0.2919	0.0448	0.5973	0.3579	1754948
70-74	0.030270871	0.0759	0.7082	0.2159	0.0448	0.6632	0.2919	1296372
75-79	0.052274056	0.2884	0.5288	0.1828	0.0759	0.7082	0.2159	991844
80-84	0.106718673	0.6585	0.2032	0.1383	0.2884	0.5288	0.1828	678895
85-89	0.12860657	0.6802	0.2061	0.1137	0.6585	0.2032	0.1383	366700
90+	0.1722756	0.6946	0.1935	0.1119	0.6802	0.2061	0.1137	163519
Women								
65-69	0.018066927	0.044	0.6686	0.2874	0.044	0.7454	0.2106	1859641
70-74	0.025151063	0.0881	0.6971	0.2148	0.044	0.6686	0.2874	1428791
75-79	0.062196862	0.3097	0.5004	0.19	0.0881	0.6971	0.2148	1170205
80-84	0.095690535	0.593	0.2574	0.1497	0.3097	0.5004	0.19	904614
85-89	0.181739775	0.6624	0.2356	0.102	0.593	0.2574	0.1497	602891
90+	0.351230458	0.6738	0.2104	0.1158	0.6624	0.2356	0.102	392747
							Total:	11611167

The same steps are followed as in Example 1 but with two changes

1. Dementia prevalence from adjusted midlife obesity forecast rather than original dementia prevalence (results not in m, only in appendix)
2. Adjusted relative risk used instead of unadjusted relative risk

Step 1. Find prevalence of dementia, adjusted for midlife obesity, in risk factor reference category (≤9 years of education) for 2015 if the risk factor prevalence had not yet changed from 2011 (2011 education prevalence). Use Equation 1 for an age and sex group. For instance, to calculate dementia prevalence in men aged 65-69 years who had 9 years or less of full time education:

$P_{tot} = 0.012142017$

$N_{tot} = 1754948$

$i = 3\ (\leq 9\ years, 10-11\ years, \geq 12\ years)$

$N_{gp_1,2011} = 0.0448 \times 1754948 = 78621.6704$ (not shown in tables)

$N_{gp_2,2011} = 0.6632 \times 1754948 = 1163881.514$ (not shown in tables)

$N_{gp_3,2011} = 0.2919 \times 1754948 = 512269.3212$ (not shown in tables)

$RR_{gp_2} = 0.869838902$

$RR_{gp_3} = 0.869838902$

Giving

$$P_{gp_1} = \frac{P_{tot} \times N_{tot}}{N_{gp_1,2011} + \left(RR_{gp_2} \times N_{gp_2,2011}\right) + \cdots + \left(RR_{gp_i} \times N_{gp_i,2011}\right)}$$

$$= \frac{0.012142017 \times 1754948}{78621.6704 + (0.869838902 \times 1163881.514) + (0.869838902 \times 512269.3212)}$$

$$= \frac{21308.60845}{78621.6704 + 1012389.418 + 445591.7839}$$

$$= 0.01386735$$

Step 2. Find dementia prevalence, adjusted for midlife obesity, for other risk factor categories (10-11 years of education, ≥12 years of education) in 2015 had education prevalence not yet changed from 2011. Use Equation 2 for an age and sex group. For this example, men aged 65-69 years who had 10-11 years of education:

$$P_{gp_2} = RR_{gp_2} \times P_{gp_1} = 0.869838902 \times 0.01386735 = 0.01206236$$

Or ≥12 years of education:

$$P_{gp_3} = RR_{gp_3} \times P_{gp_1} = 0.869838902 \times 0.01386735 = 0.01206236$$

Step 3. Find number of people with dementia in risk factor reference category using education prevalence from 2015. Note – this is how change in risk factor prevalence is incorporated into the model. For this example, men aged 65-69 years with ≤9 years of education.

$$N_{gp_1,2015} \times P_{gp_1} = 0.0448 \times 1754948 \times 0.01386735 = 1090.274$$

Step 4. Calculate number of people with dementia in other risk factor categories using 2015 education prevalence. For this example, men aged 65-69 years with 10-11 years of education:

$$N_{gp_2,2015} \times P_{gp_2} = 0.5973 \times 1754948 \times 0.01206236 = 12644.133$$

Or ≥12 years of education:

$$N_{gp_3,2015} \times P_{gp_3} = 0.3579 \times 1754948 \times 0.01206236 = 7576.319$$

Step 5: Total number of people in one age and sex group.

$$1090.274 + 12644.133 + 7576.319 = 21310.726$$

Step 6: Calculate new dementia prevalence. Note – unlike in Example 1, here there is a change in dementia prevalence by age and sex group as there was a change in prevalence of education by 2015.

$$21140.08 \div N_{tot} = 21310.726 \div 1754948 = 0.01214322$$

Step 7: Repeat in each age and sex group to get total number of people with dementia in a year, here 2015.

Appendix Table A3.4: Number of people in each risk factor category in 2015

Men	$N_{gp_1,2015}$	$N_{gp_2,2015}$	$N_{gp_3,2015}$
65-69	78621.67	1048230.440	628095.889
70-74	58077.4656	859753.9104	378410.9868
75-79	75280.9596	702423.9208	214139.1196
80-84	195793.318	358999.676	124102.006
85-89	241471.95	74513.44	50714.61
90+	111225.6238	33701.2659	18592.1103
Women			
65-69	81824.204	1386176.401	391640.3946
70-74	62866.804	955289.6626	410634.5334
75-79	103095.0605	815749.9055	251360.034
80-84	280158.9558	452668.8456	171876.66
85-89	357514.363	155184.1434	90252.7827
90+	260155.6128	92531.1932	40060.194

Appendix Table A3.5: Repeating methods above for each age and sex group gives the results in this table. The above results coincide with the first row of results for men aged 65-69 years

	Step 1	**Step 2**	**Step 2**	**Step 3**	**Step 4**	**Step 4**	**Step 5**	**Step 6**
Men	P_{gp_1}	P_{gp_2}	P_{gp_3}	**≤9 years education dementia cases**	**10-11 years education dementia cases**	**≥12 years education dementia cases**	**Number with dementia**	**New dementia prevalence**
65-69	0.01386735	0.01206236	0.01206236	1090.274187	12644.1331	7576.3188	21310.72606	0.012143224
70-74	0.034409739	0.02993093	0.02993093	1998.430443	25733.2339	11326.193	39057.85699	0.030128587
75-79	0.057610051	0.050111463	0.050111463	4336.939886	35199.4904	10730.825	50267.25487	0.050680606
80-84	0.111682983	0.097146203	0.097146203	21866.78184	34875.4556	12056.039	68798.27614	0.101338611
85-89	0.134192398	0.116725768	0.116725768	32403.7	8697.63852	5919.7018	47021.04032	0.128227544
90+	0.179407254	0.156055408	0.156055408	19954.68369	5259.26482	2901.3994	28115.34787	0.171939333
Women								
65-69	0.020634569	0.017948751	0.017948751	1688.407167	24880.1346	7029.4558	33597.99758	0.018066927
70-74	0.028538397	0.024823808	0.024823808	1794.117818	23713.9272	10193.513	35701.55783	0.02498725
75-79	0.06833042	0.059436458	0.059436458	7044.528805	48485.2848	14939.95	70469.76359	0.060220016
80-84	0.101034084	0.087883377	0.087883377	28305.60353	39782.0668	15105.101	83192.77158	0.091964939
85-89	0.190092912	0.16535021	0.16535021	67960.94621	25659.7306	14923.317	108543.9934	0.180039167
90+	0.366804443	0.319060774	0.319060774	95426.23452	29523.0741	12781.636	137730.9451	0.35068618
						Total:	723807.5313	0.062

Points to note:

- Prevalence of dementia from the obesity forecast used instead of original dementia prevalence
- In combined forecasts prevalence in each current risk factor category (in this example education) does change, but only as it is adjusting for other risk factors (in this example midlife obesity)

A4: Questions from CamCAN used to create variables

A4.1 Home interview

Marital status (home interview Q5):

5	DG4	What is your marital status?	1. Single (never married) 2. Married / civil partnership 3. Co-habiting 4. Divorced/ separated 5. Widowed		

Self-perceived health (home interview Q321):

321	HC1	Would you say for someone of your age, your own health in general is	1. Excellent 2. Good 3. Fair 4. Poor 7. Don't know 8. No answer 9. Not asked		

Overall social class (home interview Q37):

37	EM8	What is (was) the full title of your main job	Text answer		

Overall education (home interview Q73):

73	DG16	Which of the following qualifications do you have? (YOU CAN SELECT MORE THAN ONE)	1. College or university degree or higher 2. A levels/AS levels or equivalent 3. O levels/GCSEs or equivalent 4. CSEs or equivalent 5. NVQ or HND or HNC or equivalent 6. Other professional qualifications e.g.: nursing, teaching 0. None of the above 8. No answer		SHOW CARD DG16

A4.2 Self-completion questionnaire

A4.2.1 Employment

Questions on employment were asked once for every participant.

EMPLOYMENT

You will be asked about the **main jobs** that you have undertaken for different periods of your life. The enclosed guide gives examples of job titles and how we will code them. Please enter this sort of title. We also ask for the number of people you employed, or supervised during that period.

Age	**SOC number (1-10) or JOB TITLE**	**Number of people in charge of**
18-19	Not employed	
20-24	Shop assistant	0
25-29	Secretary	0
30-34	Legal secretary	2
35-39	Personnel assistant	2
40-44	Human resources manager	>10
45-49	Human resources manager	>10
50-54	Human resources manager	>10
55-59	Human resources manager	>10
60-64	Human resources manager	>10
65-69	Retired	0
70-74		
75 years and above		

Please enter the job titles below, please try and be as explicit as possible. If you were in charge of people please indicate the approximate number. If you are not sure of the code enter your job title in the box provided.

Age	**SOC number (1-10) or JOB TITLE**	**Number of people in charge of**
18-19		
20-24		
25-29		
30-34		
35-39		
40-44		
45-49		
50-54		
55-59		
60-64		
65-69		
70-74		
75 years and above		

A4.2.2 Education

Questions on education were repeated specifying for age groups 13 to 29 years (young adulthood), 30 to 65 years (midlife) and 65 years and above (later life) depending on the age of the participant.

TRAINING

The following questions apply to the time in your life between the ages 13 and 29 years of age.

Please detail all types of training or study undertaken from age 13 to 29

Type of Course	**Number of years completed**	**Full or part time**
CSE		
NVQ level 1 / BTEC Introductory		
O level / GCSE / leaving certificate		
NVQ level 2 / BTEC First diploma		
A level / International baccalaureate		
NVQ level 3 / BTEC Diploma		
HNC / HND / NVQ level 4 / BTEC Professional		
BTEC Advanced		
College diploma		
University Undergraduate		
University Masters		
University PhD / Doctorate		
Clerical, administrative or book-keeping course		
Business course		
Trade apprenticeship		
Other professional course (specify)		
Other technical course (specify)		
Other graduate course (specify)		
Any other course (specify)		

A4.2.3 Activities

Questions on activities were repeated specifying for age groups 13 to 29 years (young adulthood), 30 to 65 years (midlife) and 65 years and above (later life) depending on the age of the participant.

ACTIVITIES

Did you travel to any of the following places between the ages of 13 and 29?
Please tick (✓) all that apply

- ○ Around the UK/Ireland away from where I lived
- ○ Southern Europe (e.g. Italy, Spain)
- ○ Northern Africa / Middle East (e.g. Tunisia, Egypt)
- ○ North America (e.g. USA, Canada including Alaska, Hawaii)
- ○ Australia / New Zealand / Pacific Islands / Antarctica (e.g. Fiji, Togo)
- ○ Northern Europe /Scandinavia (e.g. France, Germany, Norway, Greenland)
- ○ Eastern Europe (e.g. Russia, Romania)
- ○ Southern Africa / Asia (e.g. Kenya, Madagascar, Mauritius, China, India)
- ○ South America / Central America /Caribbean (e.g. Mexico, Cuba, Brazil)
- ○ None of the above

From the ages of 13 to 29 please indicate how often you ever did the following activities (please tick ✓ box)

Type of activity	**Never**	**Less than once a month**	**Once a month**	**Every two weeks**	**Every week**	**Daily**
Make an outing to see a family member, friend or group of friends						
Practise or play a musical instrument						
Practise or develop an artistic pastime (e.g. drawing, acting, writing etc.)						
Mildly energetic activities (e.g. walking, carpentry, gardening, housework)						
Moderately energetic activities (e.g. dancing, golf, lawn mowing, easy cycling)						
Vigorous energetic activities (e.g. running, squash, competitive tennis)						
Read (material or any sort)						
Speak a second language						
Computer games / games consoles						
Social networking / internet surfing						
Crossword puzzles / sudoku						
Strategic games (e.g. chess)						
Prayer /religious activities						